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CHRONIC HEMOLYTIC ANEMIA WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA.

By Louis P. Hamburger, M.D.,
ASSOCIATE IN MEDICINE, JOHNS HOPKINS SCHOOL OF MEDICINE,
AND
Alan Bernstein, M.D.,
ASSISTANT IN MEDICINE, JOHNS HOPKINS SCHOOL OF MEDICINE,
BALTIMORE, MD.

(From the Medical Clinic, The Johns Hopkins Hospital.)

I.

The passage of blood-stained urine engaged the attention of the earliest medical observers. Both Hippocrates[1] and Galen[2] attributed an evil prognosis to the occurrence of black urine. The term included not only hematuria but probably, hemoglobinuria as the modern title "black water fever" suggests. However, it was not until 1883 that Ponfick[3] differentiated hematuria from hemoglobinuria and determined that the latter resulted from an antecedent hemolysis and hence, from hemoglobinemia. While all hemoglobinurias dependent on intravital hemolysis have many clinical features in common, the causes have been classified for purposes of discussion as exogenous and endogenous.

The hemoglobinurias of exogenous origin are associated with infections and intoxications and are discussed in the monographs devoted to the subject. Recently, a new member was added to this group when the discovery was made that the consumption of fish or eels containing resinous acids was followed by a malady, a feature of which is "hemoglobinuria."

The disorder is indigenous to the environs of Königsberg in Germany and is known as Haffkrankheit.[4]

Poisonous resinous acids are a byproduct of the cellulose factories of Königsberg and find their way through drainage into a nearby inlet or "Haff." All the fish and certain eels in the inlet ingest the poisonous acids and become "Haff sick." If these fish containing the resinous acids are eaten by the villagers living adjacent to the water or by their cats, cats and human beings are taken ill with this singular malady.

In man the Haff disease manifests itself by the appearance of "hemoglobinuria" and by a disorder of the musculature characterized by severe pain, stiffness and limitation of movement. The attacks have a remarkable tendency to appear paroxysmally. If the disorder leads to death necropsy discloses degeneration of the striped muscles.

The manifestations of the disease have been produced experimentally by feeding resinous compounds to fish. Cats fed on these fish also become ill and develop "hemoglobinuria" and progressive impairment of gait. At autopsy the striped muscles are grayish-red and resemble fish flesh.

We shall see later how greatly this curious Haff disease resembles a rare variety of so-called paroxysmal hemoglobinuria appearing spontaneously in man.

While referring to hemoglobinurias of exogenous origin another pertinent syndrome little known in this country should be mentioned. It is favism. In 1933, we became indebted to Thomas McCrae and J. C. Ullery[5] for the only report of a case in the English language. Favism is caused by inhalation from blossoming bean plants of the species *vicia fave* or by ingestion of the beans, either raw or cooked. It occurs most frequently in Sicily and southern Italy. The most spectacular feature of favism is the sudden occurrence of hemoglobinuria. The symptom complex includes, however, prostration, fever and acutely developing anemia and jaundice.

Since in animal experimentation with the offending bean an anaphylactic reaction has been obtained after the animals had been previously sensitized, it has been suggested that the symptoms in man represent a hypersensitiveness to the protein of the bean and its blossom.

While the hemoglobinuria of favism is exogenous in origin, so far as the introduction of the blossom or bean into the body is concerned, there is likewise an endogenous mechanism in operation productive of the anaphylaxis which is assumed to be responsible for the disorder. Therefore, this variety of hemoglobinuria may be viewed as a transition from the exogenous to the endogenous group of hemoglobinurias which we shall now proceed to review.

II.

An endogenous causal factor is evidently the important element in the mechanism provocative of certain hemoglobinurias classified in the foreign literature as the paroxysmal hemoglobinurias.

In this country paroxysmal hemoglobinuria has been used synonymously with hemoglobinuria provoked by chilling. However, the term as used in the comprehensive German reviews includes 3

types, namely, cold, march and the so-called paralytic hemoglobinurias. A new fourth type was added when, in 1931, Micheli[6] described a well defined clinical entity a prominent feature of which was paroxysmal hemoglobinuria. The description concerned a patient whom he as well as Marchiafava[7] had seen from time to time. It is this form which the title of the present communication describes. During paroxysms, perhaps all 4 but at least 3 of these types have in common, hemolysis leading to hemoglobinemia and hemoglobinuria. Nevertheless, the exciting cause of the attack, when demonstrable, varies in these several types of paroxysmal hemoglobinurias and together with their clinical manifestations justifies their separation.

In respect to causative factors cold hemoglobinuria is best understood. Mackenzie[9] traces the historic development of our knowledge of the 3 criteria by which this form of paroxysmal hemoglobinuria is usually differentiated: syphilis, chilling and the presence of the Donath-Landsteiner test.

The march variety as its name suggests follows excessive bodily exertion, particularly that involved in walking or marching. Fleischer[10] described it first, in 1881, in the case of a soldier who after a long march suddenly voided a typically hemoglobinuric urine. The only report of a well studied case in English is that of Watson and Fischer[11] of London, Canada. These authors suggest that march hemoglobinuria "is an exaggeration, exemplified in certain predisposed individuals, of a more or less naturally occurring phenomenon." As corroborative evidence they call attention to the observations of Feigl[12] who found blood pigment in the serum and urine of more than half of 27 men after an army pack march of 35 kilometers. The lordotic position has been considered a decisive factor with the implication that there exists some relation between march hemoglobinuria and orthostatic albuminuria.

Not to be disregarded is the suggestion of Watson and Fischer that there is an affinity between march hemoglobinuria and the so-called paralytic hemoglobinuria that has been observed in both man and beast. The modifying epithet "so-called" is used advisedly because the discoloration of the urine in these cases has been demonstrated to be due to myoglobin, a constituent of muscle fibers, rather than to hemoglobin. Paroxysmal paralytic myoglobinuria plays a more important rôle in equine than in human pathology. The similarity of some of the clinical features and especially the resemblance of the degenerative changes in the muscles of the horse and of the few human victims of the disease warrant a short digression into veterinary medicine.

The recognition of equine "hemoglobinuria" now generally classified as myoglobinuria, antedates by many years the discovery of an analogue in human clinical pathology. The pioneer work in this line is Bollinger's contribution in 1877.[13]

Still known as "hemoglobinuria" among many veterinarians the disorder affects previously healthy, vigorous horses who have stood resting in their stalls for one or more days, but who are still feeding on their usual diet. After such a "holiday," they are taken out to work one morning when within a few minutes, the susceptible horse exhibits stiffness and lameness in one or both hind legs; urged on, the legs lose power rapidly and the animal finally sinks to the ground. Coincidentally there may be muscular twitching, sweating, dyspnea and fever. The most striking accompaniment is the dark red, "hemoglobinuric" urine. Death may ensue in the course of a few days. If a fatal issue does not take place, a residual paralytic condition with atrophy may remain for weeks, months or years. Nevertheless, complete regeneration may eventually take place. The animal that has recovered may suffer from repeated attacks; the affection is truly a paroxysmal, paralytic "hemoglobinuria." At autopsies, the muscles involved are very pale, edematous and of a grayish-yellow color like "fish flesh."[14]

Directing attention to the parallelism of equine paralytic hemoglobinuria with the condition he was recounting, Meyer-Betz,[15] in 1910, described the case of a boy who exhibited a peculiar type of "hemoglobinuria" associated with widespread muscular paralyses.

The boy, aged 13, was admitted to Friedrich Müller's Clinic in November, 1909, in a state of collapse. Two days after an attack of abdominal pain he voided urine which was black in color. Annually, since his tenth year he had had one or two such paroxysms accompanied by great muscular weakness. In 1907, it was noted that in addition to the discolored urine the shoulder girdle muscles were atrophic, the gastrocnemius muscles were large and hard. The diagnosis was recorded as "progressive muscular dystrophy of the hypertrophic type." In 1909, following another attack of "black urine," the muscular disability while marked was "rather better than worse." The diagnosis was revised to read "muscular dystrophy." Later in the year he suffered an attack of muscular weakness "of such a degree that he appeared moribund." The urine was bloody. From such a serious state his improvement was rapid and spectacular. This time the diagnosis was hemorrhagic nephritis and muscular dystrophy. Finally, Meyer-Betz correctly evaluated the "hemoglobinuria" and differentiated the muscular paralyses and contractures from those of the classic dystrophies. The boy recovered in a few months with only a residual contracture of the right Achilles tendon.

Since Meyer-Betz' publication only 3 similar cases have been reported: Günther's[16] (1924), Paul's[17] (1924) and Hittmair's[18] (1925). Autopsies in both Günther's and Paul's cases yielded pathologic evidence to complete the resemblance between the equine and human types of paralytic "hemoglobinuria:" the affected muscles resembled "fish flesh!" It will be recalled that the same descriptive term was used to characterize the appearance of the muscles of cats and men dead of Haff disease. In all these paralytic disorders accompanied by abnormally colored urine the pigment is apparently derived entirely or in greater part from the muscles. This origin is suggested by the pallor of the muscles to which repeated reference has been made. Secondly, anemia of any noteworthy degree such as would result from hemolysis is absent. Most important testimony of all has been afforded by the spectroscopic

disclosure of myoglobin in the blood and urine in the equine disorder[19] and in the Haff disease of man.[20]

Although the term "hemoglobinuria" persists in the literature of these paralytic maladies under consideration, all recent writers consider it a misnomer for which myoglobinuria should be substituted. It would be interesting to apply this precise spectroscopic technique to the investigation of future cases of typical or atypical paroxysmal hemoglobinuria especially of the march variety to determine if perchance, myoglobin may share in the discoloration of the urine.

III.

Reverting to the statement that the discussion in the monographs devoted to the paroxysmal hemoglobinurias in man was limited to the cold, march and paralytic varieties it will be recalled that, in 1931, Micheli added what a German author[8] subsequently called "the fourth form." This form Micheli established from a study of 13 cases described here and there in many languages, including one in English.[26] Three more references to the newly recognized syndrome were given by Rosenthal[8] in his paper published in 1932. He added a 17th case of his own and stimulated a pupil, Rudolf Meyer,[21] to write an inaugural dissertation on the subject in 1933. An 18th case is included in the dissertation. Two further examples of the "new form of paroxysmal hemoglobinuria" have since been published and we shall now proceed to summarize an account of the course of this disorder in each of 2 patients who have been under our observation.

Case 1.—The patient, now a married woman, is at the present time (1936) 28 years of age. She has been under observation intermittently for a little over 10 years for a disorder which first manifested itself by the passage of darkly colored urine at the age of 18.

Her mother and brother were subject to hay fever.

The patient's medical history had been previously uneventful.

In mid December, 1925, she observed after an attack of abdominal pain the discoloration of the urine just mentioned. The following night she made a similar observation. When examined several days later pallor of the skin and mucous membranes was noted; a systolic murmur, maximum over the pulmonic area, was heard; the abdominal examination was negative. The urine was dark amber, contained a trace of albumin and an occasional pus cell.

The patient was not seen again until September, 1926, when she complained of fatigability. There was a history of repeated transient darkening of the urine. A distinct anemia had developed. The red blood cells numbered 3,400,000; hemoglobin 49%; leukocytes, 4950 with a normal differential count. During the latter part of the year there were a number of paroxysms of what was now recognized as hemoglobinuria. The attacks lasted a few days during which the urine was at times almost black by reflected light and a deep Burgundy red by transmitted light. Two of the paroxysms of this period were preceded by upper respiratory infections. Icterus was now evident.

Throughout most of the year 1927 the young woman led a fairly active life. She reported that often 2 or 3 days before a menstrual period mahogany colored urine was voided. The relation to the menstrual cycle was not invariable. It was observed, however, that the most deeply pigmented urine was always voided during the night and early morning hours.

After a severe attack of hemoglobinuria prolonged to 2 weeks she entered this hospital (Unit No. 9216) on November 16, 1927. She had lost no weight, the skin and mucous membranes were pale. The sclerae were tinged a light yellow. Inspection of the rhinopharynx revealed nothing abnormal. The cervical lymphatic glands were not enlarged. The lungs were clear. The systolic murmur previously noted was present. Blood pressure 128/48 mm. Neither the edge of the liver nor the spleen was palpable. The basal metabolic rate was +16. The blood smear revealed marked anisocytosis and poikilocytosis; no nucleated red blood cells were seen. Reticulocytes were 10%. The fragility of the red blood cells was normal. The Wassermann reaction was negative. The Donath-Landsteiner test was likewise negative. The blood non-protein nitrogen was 36 mg.%; sugar, 92 mg.%, cholesterol, 175 mg. %. The patient's blood was of Group II (Moss). Roentgenologic examination discovered a non-union of the base of the sacrum.

During the 3 weeks following admission to the hospital there were 2 paroxysms of hemoglobinuria of several days' duration. In some specimens of the urine red blood cells were discovered; hemoglobin and methemoglobin were demonstrated. During these attacks of hemoglobinuria auto- and isohemolysins were found in the blood only to disappear when the paroxysms had terminated.

In 1928, there was little subjective evidence of illness but the anemia persisted in varying degree, the icteric hue fluctuated, paroxysms of hemoglobinuria were frequent—all in spite of many vain efforts to prevent the attacks. The patient's activities were limited; exposure to chilling was avoided; she was given iron, arsenic, liver and potassium iodid. In the summer of 1928 an attack of hemoglobinuria lasted almost 2 months.

In January, 1929, phlebitis supervened. The left saphenous vein was affected. During the year the hemoglobin never rose above 60%; in the acute seizures it fell as low as 30%. There were infrequent attacks of pain in the right lateral abdominal region, sometimes accompanied by vomiting.

For two months of the winter of 1930 the patient was the victim of a psychosis characterized by delusions of persecution and sex obsessions. From the mental disturbance she made a complete recovery.

Having become so familiar with the characteristic features of her disorder she rarely sought medical advice during the next 4 years. In 1933, she married and cared for her own household.

For a particularly severe paroxysm of hemoglobinuria in June, 1934, she was once more admitted to the hospital. This attack was accompanied by precordial distress, the temperature rose to 102°; the pulse, 120. The red blood cells numbered 1,280,000; hemoglobin, 39%; leukocytes, 2500. The mean corpuscular volume was 90 cu. microns. There was definite jaundice. The icterus index was 16. Although the exacerbation was severe, it lasted only 3 days.

In September, 1935, the condition was complicated by the appearance of cystopyelitis. For about 4 months she had recurring attacks of fever with a maximum of 105°. The pyrexia was attributed to the urinary tract infection with the colon bacillus. In spite of the repeated febrile seizures there was only one severe paroxysm of hemoglobinuria occurring in October and lasting less than 24 hours. The hemoglobin fell to 25%. Since this attack hemoglobinuria has not returned but oxyhemoglobinemia and urobilinuria have been demonstrated repeatedly. In this period, too, comprehensive skin sensitization tests were undertaken without significant

results. The urine has contained albumin, pus cells, a few red blood cells and granular casts. The casts and amorphous detritus were stained yellow: the pigment gave the Prussian blue reaction for iron. The stool exhibited an excess of urobilin.

At present (February, 1936) while pyuria persists, there is no fever and the hemoglobin registers 60%. The subject of this extraordinary medical history has resumed her household duties and is leading a fairly normal life.

CASE 2.—An automobile mechanic, white, aged 29, was admitted to this hospital (Unit No. 48198) on March 9, 1933, complaining of attacks of discoloration of the urine and weakness of one year's duration. The patient's general health had been good.

A dark discoloration of the urine was first noted a year before admission. Subsequently there were frequent nose bleeds and hemorrhages from the gums. The patient became weak and tired readily. Dyspnea and tachycardia on exertion were prominent. There were occasional vague pains beneath the sternum. Four months before entry the symptoms were aggravated, at which time the patient observed that his urine was dark brown in the morning.

On admission his temperature, pulse and respiration were normal. Blood pressure was 120/65 mm. The skin had a yellowish tint; there was pallor of the mucous membranes. His heart was normal except for the presence of a systolic murmur. Neither the liver nor spleen was felt.

The erythrocyte count was 2,790,000; hemoglobin 62%, leukocyte count 4050; neutrophils 63%, lymphocytes 33%, monocytes 4%, an occasional normoblast was found. The mean corpuscular volume of the red blood cells was 104 cu. microns. Platelets, reticulocytes, bleeding time, clotting time and clot retraction were normal. The blood was Group IV (Moss). The Wassermann reaction was negative. In the urine albumin was present from time to time, frequently in considerable amounts. Urobilin was found almost constantly. The benzidin test was often positive. Microscopically, there were observed a few white blood cells and a rare hyalin cast as well as small brownish granules in profusion, both intra- and extracellular, the exact nature of which was not determined. Non-protein nitrogen was 28 mg. %; Van den Bergh test, 1 mg. %. The gastric juice revealed free hydrochloric acid after the injection of histamin. Roentgenologic examination showed non-union of the top of the sacrum.

During the patient's stay of 4 months in the hospital there occurred 3 spontaneous attacks of hemoglobinuria. Spectroscopic examination confirmed the presence of hemoglobin in the urine. It was noted repeatedly that the specimen voided between midnight and 6 A.M. was much darker and gave a more positive benzidin reaction than the day specimens. That this was not a phenomenon of simple concentration was proved by forcing liquids during the night so that the nocturnal output equalled or exceeded the diurnal. Under these circumstances the greatest excretion of pigment still occurred at night. After the attacks of hemoglobinuria the patient became jaundiced with an icterus index as high as 20. The Donath-Landsteiner test was repeatedly negative. During the exacerbation of hemoglobinuria early in May the liver became palpable. Further studies of the blood determined that the fragility was normal. Just after the onset of the first attack of hemoglobinuria reticulocytes rose to 10.4%.

Therapy directed toward the anemia produced only transitory improvement. Several bouts of hemoglobinuria occurred during the next few months. Thus, he continued until January, 1935, when he entered the Memorial Hospital in Richmond. Allergic studies made at this time were negative.

In March, 1935, he was transferred to the Hospital of the University

of Pennsylvania.* Red blood cells were 1,900,000; hemoglobin, 31%; leukocytes, 9000 with a normal differential count; reticulocytes, 37%. Hemolysis began at 0.50% salt solution and was complete at 0.35%. With the hope of favorably influencing the hemolytic process splenectomy was performed on April 15, 1935. Before operation two transfusions were followed by severe reactions with fever and hemoglobinuria; while postoperative transfusions proceded uneventfully without any unpleasant sequelæ. The spleen weighed 360 gm.; the sinuses contained a moderate amount of blood, the splenic pulp was normal.

A few days after splenectomy the patient developed otitis media and mastoiditis for which mastoidectomy was performed. A streptococcus septicemia supervened. From these he recovered, so that in September, 1935, he was discharged improved but continued to have paroxysms of hemoglobinuria and was still markedly anemic.

The patient's present condition (December, 1935) is aptly expressed in his own words: "On my best days, the urine is black only in the morning; on the worst, it is black throughout the entire 24-hour period."

With the addition of these 2 cases, 22 examples of a peculiar disorder accompanied by paroxysmal hemoglobinuria are now recorded† (Table 1). From the first case published by Chauffard and Troisier,[22] in 1908, to the present day the disorder under consideration has received many titles. Marchiafava[7] called it "anemia emolitica con emosiderinuria perpetua;" Hijmans van den Bergh[23] had named it "ictère hémolytique avec crises hémoglobinuriques;" Enneking,[31] "hemoglobinuria paroxysmalis nocturna" while Rosenthal commemorating the basic work of Marchiafava and one of his collaborators, suggested the Italian's title, adding "of the Marchiafava-Micheli type." We venture to describe the symptom complex as chronic hemolytic anemia with paroxysmal nocturnal hemoglobinuria. The title implies the prolonged duration of the disorder, the fundamental hemolytic state and the characteristic attacks of hemoglobinuria. It does not include the term icterus which is a concomitant of the hemolysis, because its inclusion may perpetuate the confusion with well known forms of hemolytic jaundice from which it should be separated. In the interest of brevity we shall hereafter often refer to the condition as chronic hemolytic anemia.

Chronic hemolytic anemia chiefly affects males. Of the 22 patients under consideration only 6 are women. The age incidence of onset lies chiefly in the third and fourth decades; the youngest is Scheel's[27] patient of 15, while the oldest is Salén's[29] who was 47 years of age.

In none is there a family history of the disease or of any allied disorder. Previous illnesses apparently play no predisposing part: neither syphilis nor malaria is a causal factor. The onset is insidious; increasing pallor and varying degrees of jaundice are usually the first signs of ill health. Pain in the abdomen and back may be the initial symptom.

* The patient was admitted on the service of Dr. O. H. P. Pepper, to whom we are indebted for the privilege of quoting from his records.

† Since this paper was written two additional references to case reports of this malady have come to our attention: Falkiewicz, A., and Musial, W., Klin. Wchnschr., **14**, 1078, 1935, and Trestini, S., Policlinico (Sez. med.) **42**, 550, 1935.

TABLE 1.—SUMMARY OF DATA CONCERNING REPORTED CASES OF CHRONIC HEMOLYTIC ANEMIA WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA.

Case.	Authors.	Date of report.	Sex.	Age at onset.	Symptom of onset.	Duration of disease at time of report (years).	Operations.	Outcome at time of report.
1	Chauffard and Troisier[22]	1908	M.	"Young"	Abdominal pain and jaundice	6	Cholecystostomy	Living.
2	Hijmans van den Bergh[23]	1911	M.	35	Jaundice	12		Living.
3	Marchiafava and Nazari[24]	1911	M.	23	Abdominal pain and jaundice	8	Cholecystotomy	Died of "grippe."
4	Biffis[25]	1915	M.	25	Weakness and jaundice	3	Splenectomy	Died after operation.
5	Giffin[26]	1923	F.	28	Jaundice	3	....	Living.
6	Scheel[27]	1925	F.	15	Anemia and jaundice	2	....	Living.
7	Manini[28]	1927	M.	43	Jaundice	1	....	Living.
8	Salén[29]	1927	M.	47	Weakness, jaundice and hemoglobinuria	4	Nephrotomy	Died of pneumonia.
9	Villa[30]	1928	F.	17	Abdominal pain and enlarged spleen	5	....	Living.
10	Enneking[31]	1928	M.	37	Lumbar pain	1	....	Died of mesenteric thrombosis.
11	Saxl[32]	1928	M.	36	Hemoglobinuria	"Years"	Splenectomy	Living.
12	Barta and Görög[33]	1929	M.	34	Lumbar pain and anemia	1	Splenectomy	Died after operation.
13	Donati[34]	1930	M.	28	Chills, fever and hemoglobinuria	8	Splenectomy	Living.
14	Marchiafava[7] and Micheli[6]	1931	M.	22	Anemia	9	Splenectomy	Died.
15	Hitzenberger[35]	1931	F.	32	Anemia and jaundice	3	....	Living.
16	Nazari[36]	1931	M.	19	Weakness and anemia	1	....	Living.
17	Bergmark[37]	1931–1932	M.	34	Abdominal pain, anemia and jaundice	6	Appendectomy; cholecystectomy	Died after operation.
18	Rosenthal[5]	1932	M.	19	Chills, fever and hemoglobinuria	33	Splenectomy	Died after operation.
19	Iglauer and St. Frenreisz[38]	1934	M.	38	Jaundice and hemoglobinuria	4	....	Living.
20	Schally[39]	1935	F.	25	Anemia	4	Splenectomy	Living.
21	Hamburger and Bernstein	1936	F.	18	Hemoglobinuria	10	....	Living.
22	Hamburger and Bernstein	1936	M.	28	Hemoglobinuria	4	Splenectomy	Living.

Soon or late there are added to the anemia and icterus, paroxysms of hemoglobinuria. In our 2 patients the discoloration of the urine led them to seek medical advice. On the other hand, years may pass before the inception of evident hemoglobinuria.

Once the syndrome is established the symptoms and signs are subject to remissions and exacerbations. The therapeutic measures now at our command do not prevent the patient from remaining anemic and icteroid though able to carry on his activities in a modified way. However, without obvious cause he will suffer from sudden attacks during which the anemia increases, the conjunctivæ and skin will assume a deeper yellow color. Chills and fever may be accompaniments. He may be annoyed by precordial distress or by abdominal and lumbar pain. The patient is prostrated and temporarily disabled. When hemoglobinuria is superadded it varies greatly in intensity and duration. It may be represented merely by a reddish discoloration or the urine may be almost black. The discoloration may be brief: only the urine voided during one night or in the early morning hours may exhibit it, the hemoglobinuria ceasing during that day. On the other hand, hemoglobinuria may continue for days or weeks on end, only to disappear until the onset of another paroxysm. The nocturnal appearance or exaggeration of the hemoglobinuria in some attacks was repeatedly commented upon while our 2 patients were under our care. Subsequently we discovered that many others had made the same observation. We have stated that Enneking was so impressed by the nocturnal rhythm of the hemoglobinuria that he expressed it in the title which he gave to the disorder. In the case of Rosenthal's patient, spontaneous hemoglobinuria disappeared in the last 4 years of his life. This patient illustrates the maximum duration of the disorder. Beginning at 19 the illness lasted 33 years, death ensuing a few hours after splenectomy had been performed.

Splenectomy accounted for 3 of the 8 deaths in the series of 22 cases. Removal of gall stones from the common duct was followed by a fatal issue in 1 case. One patient died suddenly of mesenteric thrombosis; while 1 succumbed to pneumonia and another to "grippe." Fourteen were alive from 1 to 12 years after the onset of the disease.

In addition to the characteristic symptoms and signs of chronic hemolytic anemia to which we have referred, there are some inconstant findings. Thus, the size of both the liver and spleen varies in different individuals, and in the same individual at different times.

Considering the persistent anemia it is not remarkable that venous thromboses are frequent. Both our patients suffered in the course of their illnesses from thrombosis of peripheral veins. Others have recorded the same process in the portal and intracranial vessels.

Examination of the blood reveals an anemia which may attain an extreme degree. The hemoglobin may fall as low as 15%; the

red blood cells, below a million. Reticulocytosis is almost constantly present with a marked elevation after one of the hemolytic crises. The mean corpuscular volume of the red blood cells in our 2 cases was normal or slightly increased. The cellular diameter corresponded approximately with the volume, so that there is no spherocytosis such as accompanies hemolytic icterus. Fragility of the erythrocytes is normal or slightly increased. The leukocytes may be normal in number but leukopenia is the rule during attacks; the count may be as low as 2000 with a relative lymphocytosis. The platelets are usually moderately decreased. Hemoglobinemia is constantly found. During the paroxysms bilirubinemia increases.

In these paroxysms the presence of varying amounts of hemoglobin in the urine is obvious to inspection. Its increase in the night specimens has already been stressed. Albuminuria and urobilinuria are constantly demonstrable. Marchiafava was the first to emphasize the presence of considerable hemosiderin in the centrifugate. Regarding it of great diagnostic importance it will be remembered that his designation for the disease reads "hemolytic anemia with perpetual hemosiderinuria." This iron-containing substance accounts for the yellowish-brown pigmentation of the casts, cellular elements and amorphous débris almost constantly detectable in the centrifugate.

A quantitative estimate of urobilin in the stools yields a high value.

IV.

Sufficient evidence has already been presented to differentiate chronic hemolytic anemia with paroxysmal nocturnal hemoglobinuria from other paroxysmal hemoglobinurias. Likewise, there are sufficient clinical data to separate the disorder from congenital or acquired hemolytic icterus. They include the absence of a hereditary factor, the infrequency of splenic enlargement, the therapeutic failure of splenectomy. Other differential diagnostic criteria are the inevitability of hemoglobinuria during the course of the fully developed illness in contrast with the extreme rarity of this sign in hemolytic jaundice, the normal or slightly increased fragility of the red blood cells and the absence of the spherocytosis characteristic of hemolytic icterus.

To bear in mind the remote possibility of favism as a cause of anæmia, jaundice, fever and hemoglobinuria is sufficient to make inquiry as to the ingestion of the incriminating bean. Let it be likewise remembered that in this country the bean of the species *vicia fave* is used almost exclusively as pigeon food and cattle fodder. Finally, in discussing the differential diagnosis of the complaint under consideration, the acute hemolytic anemia of Lederer is also to be considered. The course of the disorder soon differentiates it from chronic hemolytic anemia. In Lederer's anemia transfusions

yield dramatic curative results, while if untreated, death usually follows. When recovery has occurred, there are no further paroxysms.

V.

The pathologic anatomic studies of the disorder under discussion are founded on 7 autopsies and the examination of 5 spleens removed at operation.

The studies yield evidence that this disorder can be differentiated on pathologic grounds as well as on clinical data from hemolytic icterus. While now and again as in life, the spleen was found somewhat enlarged, this enlargement was exceptional. Without exception, however, the note is made that the splenic pulp is not rich in red blood cells as in forms of hemolytic jaundice.

The tubular epithelium of the kidneys is filled with a yellowish-brown pigment which can be demonstrated to contain iron by the Prussian blue reaction. Neither the liver nor the spleen exhibits this hemosiderosis.

Gall stones, though suspected several times in life, were discovered only once, in contrast with their frequent occurrence in cases of hemolytic icterus. The bone marrow is hyperplastic.

VI.

From foregoing references to individual cases it may be concluded that chronic hemolytic anemia is compatible with life for many years. Half of the 8 deaths described in the literature followed surgical interventions. Until this syndrome received its proper nosologic status, splenectomy was performed on the assumption that the patients would receive the same benefit that accrued to those suffering from congenital or acquired hemolytic icterus. We have seen that in 8 of the 22 patients of the series the spleens were removed, and 3 died immediately after the operation. In only 1 of the 5 survivors, the patient of Donati,[34] was there an improvement that might be attributed to splenectomy. Marchiafava and Micheli have directed attention to a possible by-effect of the operation. While before splenectomy their patient tolerated transfusions badly; after the operation there seemed to be an immunity from reactions, an immunity which he lost toward the end of life. It must not be assumed that reactions invariably follow transfusions in this class of patients because both Giffin's[26] and Rosenthal's received blood without ill effect.

From the data just presented it follows that splenectomy is not indicated in the management of this group of patients. Transfusions are prone to be followed by untoward symptoms and a decision to introduce blood must be reached with this possibility in mind. Our first patient has never been transfused during the 10 years of her

disorder yet her hemoglobin which has been as low as 25% is at the time of writing 60%.

Other types of treatment were adopted by Hitzenberger.[35] In his patient the attacks of hemoglobinuria bore a close relation to the menstrual cycle. Therefore, in an attempt to modify the paroxysms irradiation of the ovaries was undertaken with the result that for 6 months there was neither a menstrual flow nor hemoglobinuria. However, the therapeutic effect was temporary. Three years later although amenorrhea had been reëstablished, hemoglobinuria recurred and strange to say still in a monthly rhythm. Since the hemoglobin excretion was chiefly nocturnal Hitzenberger caused his patient to sleep at night in a room equipped with a "sun lamp." It is said that under these conditions the hemoglobinuria and the accompanying symptoms were greatly mitigated.

Analogy warrants the use of the measures employed in treating other forms of anemia. Hence, regulation of activities, appropriate diet, adequate doses of efficient iron preparations and the intramuscular injections of potent liver extracts are indicated.

VII.

Concerning the pathogenesis of the disease little information of value is available. Schally[39] stresses the significance of a chronic sinus infection associated with his patient's illness. He suggests that in some manner the long standing sepsis influences the bone marrow so that red blood cells of inferior quality are produced. These red cells are more susceptible to hemolysis, not, however, by virtue of any change in their osmotic resistance. Accordingly, the patient's red blood cells were hemolyzed *in vitro* by her own serum as well as by a normal individual's serum. We have been unable to confirm these observations.

The serum of Enneking's patient contained both auto- and isohemolysins. In our first patient's blood an autohemolysin was encountered during one of the attacks of hemoglobinuria, to disappear at the termination of the seizure.

The phenomenon of nocturnal exacerbation of hemoglobinuria is so striking and constant as to be almost pathognomonic of this particular disorder. Attempts to counteract some of the possible influences which may act as nocturnal stimuli to the production of hemoglobinuria have brought about incomplete alleviation in only one instance. Thus, it will be recalled that partial success accompanied continuous irradiation by means of a "sun lamp" in the case of Hitzenberger's patient. Iglauer[38] failed to influence any of the symptoms by feeding the patient liberally at night and by controlling the position in which he slept. We were unable to observe any inhibiting effect on the excretion of the hemoglobin by increasing the ingestion of liquids at night.

Based on some experiments of Bingold,[40] Schally emphasizes the possible importance of the absence of catalase from the hemoglobin containing urine. He suggests that catalase in the blood of these individuals may be inactivated so that its protective action over the integrity of the red blood cell is diminished.

A suggestive clue is supplied by Salén who reports that he overcame the nocturnal rhythm of hemoglobinuria in his patient by parenteral administration of typhoid vaccine or milk. Diurnal hemoglobinuria followed the experiments regularly. Salén ventures the opinion that his observations may justify the assumption that the hemolysis involved in this disorder may be caused by some sort of "chronic autointoxication." Perhaps this vague term may cover absorption of certain substances from the gastro-intestinal tract. An allergic agent could either be present originally in the food or else appear as an intermediary product of metabolism acting through a mechanism similar to that assumed to operate in favism. An alternative hypothesis postulates the absorption of a hemolysin arising from the same sources and entering the body by the same route. Neither of our patients showed evidence of hypersensitivity to any foodstuffs by the usual skin tests but additional information might be adduced by food elimination experiments. It is our impression that the most fruitful future investigations will proceed along such channels.

VIII.

Chronic hemolytic anemia of the type herein considered is admittedly a rare disease. However, in addition to the intrinsic value of distinguishing it from the conditions which it resembles, certain other conclusions emerge from the discussion. Above all, attention should be called to the fact that in the past, errors in diagnosis have led to unwise treatment. For instance, before the true nature of his ailment was recognized Salén's patient had been subjected to nephrotomy in a fruitless effort to discover the source of hematuria. The jaundice associated with the disorder has been misinterpreted and the mistake has led to misdirected operations on the gall bladder. It should be reiterated, too, that a confusion of the disease with hemolytic icterus has led to splenectomy, a serious operation of doubtful utility in chronic hemolytic anemia. Then, too, reactions following transfusions are so regularly encountered in patients suffering from the disorder that this procedure is certainly inadvisable.

Finally, it may be conjectured that the disease exists in a benign form and certain instances thus pass completely unrecognized. It has been pointed out that while hemoglobinuria is the most conspicuous and dramatic manifestation of the disorder, it is only by a fortuitous circumstance that it occurs. When hemolysis proceeds at a sufficiently slow pace, no gross hemoglobinuria may appear, a condition which may continue for years. Under these

circumstances a patient after having undergone the usual examinations, is found to be anemic or icteric and further search for an underlying hemolysis may be conceivably abandoned. Accordingly, it seems important to suggest that in all cases of anemia of obscure origin, the blood serum should be examined for hemoglobin. Or again, individuals who respond to the transfusion of blood with unexplained hemoglobinuric reactions should be subjected to closer scrutiny to determine whether they may not suffer from a latent form of the ailment. Only by an increased watchfulness will additional examples of chronic hemolytic anemia with paroxysmal nocturnal hemoglobinuria be discovered so that improper treatment will be avoided and eventually more logical methods of therapy be applied on the basis of an etiology yet to be determined.

Summary. Two new instances of an uncommon type of chronic hemolytic anemia associated with paroxysmal hemoglobinuria are herewith presented. The urinary discoloration occurs chiefly at night. Concomitant variable symptoms and signs of the syndrome are abdominal, lumbar and substernal pain, jaundice and fever. Features differentiating the disease from other paroxysmal hemoglobinurias, hemolytic anemias, and congenital hemolytic icterus are discussed. The chief blood changes are an anemia which may become profound, reticulocytosis and perpetual hemoglobinemia. The urine always contains urobilin and hemosiderin. Therapeutic measures are of little avail but the disease is compatible with life for many years. Splenectomy is a dangerous procedure, usually without benefit. Transfusions are generally followed by untoward reactions accompanied by hemoglobinuria. The theory is advanced that the malady may result from the absorption of some material from the gastro-intestinal tract acting as an allergen or a hemolysin. It is suggested that benign forms of this type of chronic hemolytic anemia may pass unrecognized when hemoglobinuria is not a conspicuous feature.

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COMPARATIVE STUDY OF CYTOPLASMIC AND NUCLEAR CHANGES IN NEUTROPHILS IN SEVERE INFECTIOUS STATES.

By Theodore H. Mendell, M.D.,
associate attending physician, medical service no. 2, mt. sinai hospital,
David R. Meranze, B.S. (Chem.), M.D.,
pathologist and director of laboratories, mt. sinai hospital,
and
Theodore Meranze, M.D.,
assistant pathologist, mt. sinai hospital, philadelphia, pa.
(From the Wards and Laboratories of the Mt. Sinai Hospital.)

The literature on the hemogram in infection is voluminous and ever growing. In the past decade, the differential count according to the Schilling modification of Arneth's classification of neutrophils has become a routine procedure in many institutions. Numerous other simplifications of the Schilling count have been devised based on the increased formation and appearance of young neutrophils in the blood in response to an infecting agent. The value of the Schilling count is so unquestioned today that it should be regarded as indispensable in the study of infectious disease. It follows more

closely the course of the infection and presages in many instances oncoming complications with more accuracy than the total leukocyte count or the clinical impression. As infection progresses or complications occur there is an increase in the band forms and younger, immature neutrophils, often unrelated to the magnitude of the total white count. A steady rise in the band forms usually reflects extension of the infection, or pus formation. The appearance of still more immature forms, namely, myelocytes and myeloblasts, indicates an even graver state.

With but few exceptions, all the studies recorded in the literature on leukocytic changes in infection deal with nuclear changes, as recorded by the Schilling count or one of its modifications. Little attention has been devoted by contrast to the cytoplasmic alterations in neutrophils during disease states. However, since Mommsen[1] devised a staining technique which clearly and easily demonstrates these toxic or degenerative cytoplasmic changes in the neutrophils, more has been written about these important phenomena.

The degenerative changes in the peripheral neutrophil[2] consist essentially of an alteration of the staining quality of the cytoplasm, abnormal granulation, and vacuolization. With the Jenner-Giemsa stain as modified by Kugel and Rosenthal[3] the cytoplasm is transformed from its normal eosinophilic pink to a dirty gray or blue color. This is usually accompanied by the appearance of toxic granules. The latter are coarse, irregular in distribution, stain deep blue, and are oxidase negative in contrast to the fine regularly distributed oxidase positive granules seen in the normal neutrophil. In some neutrophils the granules are so large that the cell may be mistaken for a basophil. In addition the cytoplasm may be vacuolated and present a moth-eaten appearance about the periphery, another evidence of toxicity. The presence of these three changes regardless of their degree is sufficient to classify a cell as toxic and warrant its inclusion in the calculation of the Degenerative Index. Kugel and Rosenthal[3] have formulated a Degenerative Index based on these toxic changes in the cytoplasm as follows:

$$\text{Degenerative Index} = \frac{\text{Number of Degenerated Neutrophils}}{\text{Total Number of Neutrophil Cells}}$$

In a recent study[2] we enumerated the diseases in which toxic alterations of the cytoplasm of neutrophils appeared and did not appear; and the significance in diagnosis and prognosis their presence offered. In accord with other workers we found them most frequently present in severe spreading infections and sepsis; and that their greatest value lay in differentiating localized from generalized infections and in indicating development of complications. The conditions in which they occurred particularly were septicemia, bacteremia, pneumonia, peritonitis, osteomyelitis, and severe mastoid infections. From a prognostic viewpoint we were able to con-

firm Kugel and Rosenthal's observations that a high and rising Degenerative Index was usually indicative of a grave state.

The clinical importance of these toxic cytoplasmic changes in neutrophils is coming to be more appreciated; more data are accumulating concerning their presence and significance. Adler[4] has shown that often more information can be gained by their study than by estimation of nuclear shifts. Prochnow[5] states: "The hemogram in acute appendicitis is far more reliable if toxic granules are counted. The stain is not difficult and should be a routine measure. Toxic granules are the most important qualitative changes in leukocytes." Von Elsbach[6] has reported that the appearance of toxic cytoplasmic changes, namely, granules and Döhle bodies in the hemogram in appendicitis, usually means purulent appendicitis. Harkins[7] feels that a hemogram giving merely an estimate of the nuclear shift is incomplete and that to evaluate severe infections adequately, toxic cytoplasmic changes in the neutrophils should be included.

The literature is, moreover, particularly lacking in definite and exhaustive information regarding the comparative value of the cytoplasmic to the nuclear changes in neutrophils in severe infections. In the few such studies in the literature[8,9] only general comparisons have been made. Since in severe infections the prognosis is a major consideration, and since opinions concerning it are usually based on the general clinical impression and estimation of the patient's state, it was thought worthwhile to investigate the aid which both the Schilling and toxic studies offered and to compare their relative qualities in this respect.

We therefore have studied patients suffering with severe infections (septicemia, bacteremia, pneumonia, peritonitis, osteomyelitis, and severe mastoiditis); diseases which we have found to be associated with both nuclear and cytoplasmic changes. Since it is generally appreciated that single hemograms are of but limited interpretative value, we made frequent examinations (total white counts, differentials, Schilling and Degenerative Indices), during the course of each illness, with repeated comparisons with the clinical state. From these studies we attempted to determine the value of each procedure independently and any advantage which one procedure might have over the other, *i. e.*, which of the indices—the Schilling or the Degenerative—was a more delicate and reliable measure of the disease state of the patient.

For the nuclear changes we employed Farley's[10] filament non-filament modification of the Arneth-Schilling shift, in which neutrophils were divided into filament and non-filament cells, metamyelocytes and myelocytes. Farley regarded 9 non-filamented cells as an average normal and a count up to 16 non-filamented cells as the limit of the normal Schilling shift. Other authors have found higher limits of normalcy. Thus Love and Welter[11] found non-filament counts up to 25 as normal .Our findings essentially agree with

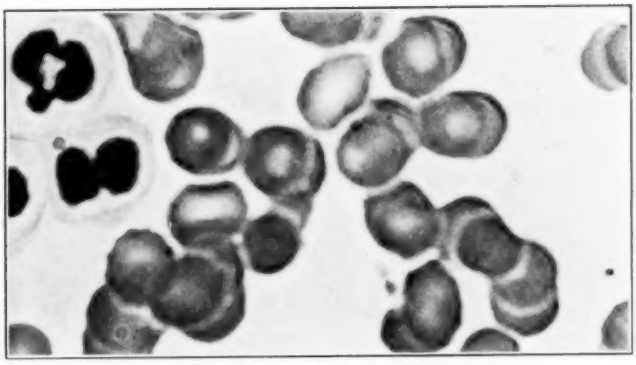

FIG. 1.—Blood smear showing cells without toxic granulation. From a case of rheumatic fever. (× 1500.)

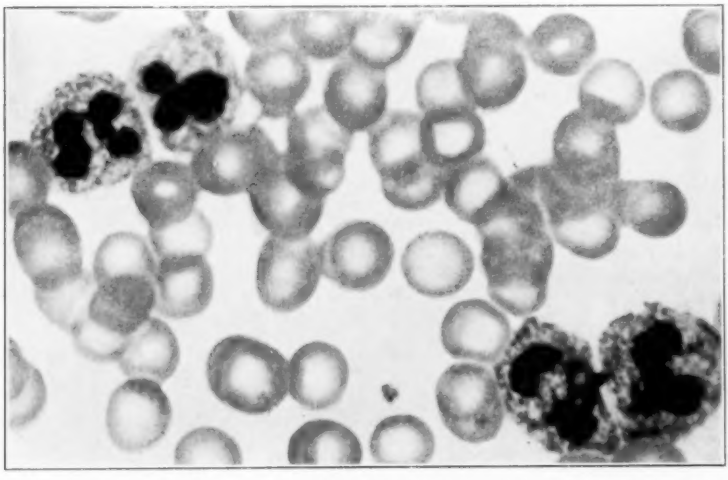

FIG. 2—Case 2. Blood smear showing cells with toxic granulations. From a fatal case of lobular pneumonia. Note all cells are toxic. (× 1500.)

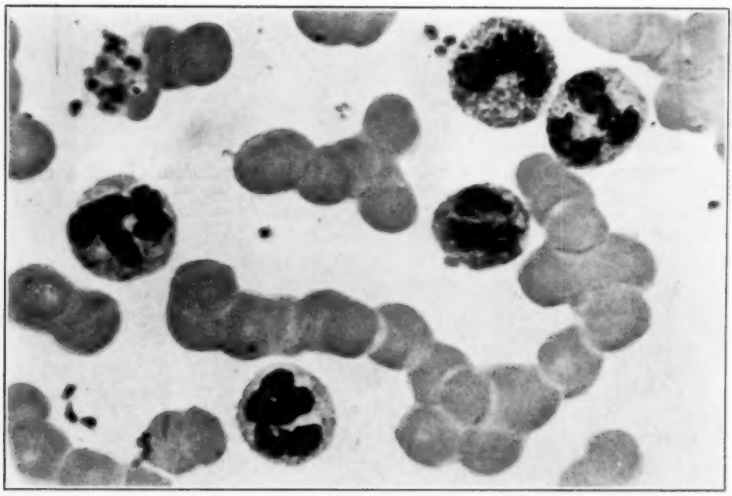

FIG. 3.—Case 16. Blood smear showing cells with some granulations. From a case of peritonitis which recovered. Note that four of the five cells are toxic. (× 1500.)

Farley's and we have therefore used his more conservative figures. Weiss[12] analyzed 20,000 Schilling indices in infection and found that staff counts of 10 or above signified a moderate shift to the left, 33 staff cells a severe shift to the left, and 41 staff cells or above a very severe shift to the left. Crocker and Valentine[13] studied 6000 hemograms in infection and found that nuclear shifts to the left of 50 cells or more are seen in the severe virulent infections in which prognosis is always guarded. In both Weiss, and Crocker and Valentine's series the severe and very severe shifts to the left were accompanied by toxic cytoplasmic changes but these were not compared with the nuclear changes. As their series of diseases demonstrating both nuclear shifts and toxic changes was essentially the same as ours, they offer a good comparison.

Based on these investigations and our experience we have looked upon non-filament counts of 8 to 16 as normal; counts of from 17 to 30 as a moderate shift to the left indicative of advancing infection; counts of 31 to 40 as a marked shift to the left and seen in severe infections; and counts of 41 or more as an extreme shift to the left seen in grave states.

For this study we classified the Degenerative Index similarly. Rosenthal and his co-workers have repeatedly shown that a persistent Degenerative Index of 90% or above usually spelled a fatal outcome, seen only in grave infections. In severe infections of lesser severity the Degenerative Index was correspondingly of a lesser magnitude. Sutro[14] has graded the Degenerative Index in infections as follows: 1+, Degenerative Index up to 25%, seen in mild infections; 2+, up to 50%, in moderate infections; 3+, up to 75%, in severe infections; and 4+, up to 100%, in grave infections. From our previous work and the above investigations we feel that a 0 to 20% Degenerative Index may be accepted as normal or indicating a mild infection; 21 to 40% Degenerative Index a moderate infection; 41 to 70% a severe infection; and 71% or above a grave infection.

With these data, therefore, a comparison between these indices becomes possible. This we have done using the following numerical limits:

Schilling Index.		Degenerative Index, %.
8–16 Non-filamented cells; normal or mild infection	(N)	0–20
17–30 Non-filamented cells; moderate infection	(M)	21–40
31–40 Non-filamented cells; severe infection	(S)	41–70
41 plus Non-filamented cells; grave infection	(G)	71–100

For this investigation we studied the first 60 cases which fulfilled our criteria of severity. These were: 1, that the disease state was known to be associated with both toxic cytoplasmic and nuclear changes; 2, that the temperature had reached 102° F. or more; and 3, that the clinical courses were alarming by their severity. In these 60 cases simultaneous Schilling and Degenerative Indices were

performed periodically during the severe phases of their infections, and compared with each other and with the clinical states of the patients to attempt to determine which index proved to be a more accurate guide of the degree of the infection.

Present Study: Division of Cases. GROUP I—29 cases (48.3%). Cases in which both the Degenerative and Schilling Indices were both positive, but in which the Degenerative Index at all times was more informative, reflecting the clinical state with a greater degree of accuracy than the Schilling count.

1. *Illustrative Case.* A. S., female, aged 59, admitted on March 20, 1935, to the service of Dr. A. Trasoff, critically ill in state of diabetic coma with massive infection and spreading necrosis of deep tissues of upper half of right thigh. She had been drowsy for 48 hours at home as the infection was progressing, then lapsed into coma prior to admission. Catheterized specimen of urine was positive for sugar, acetone, and diacetic acid; blood sugar 484 mg. per 100 cc., and carbon dioxid combining power of blood 25 volumes %. Temperature averaged 102° F. Blood urea nitrogen, blood culture and Roentgen ray examination of the infected thigh were non-informative. On forced carbohydrate and fluid intake, adequate insulin, supportive measures, and wide incisions for drainage of the infected areas she temporarily rallied, the alkali reserve rose to 56, the acidosis disappeared, the blood sugar dropped to 155 mg. level, and the diabetic condition came under control. However, the infection could not be checked, she became more septic, and in spite of repeated blood transfusions, active medical and surgical treatment she expired on April 10th of advancing sepsis. Periodic examinations during the course of her septic state comparing Schilling and Degenerative Indices are as follows:

Hb. %	R.B.C. in millions.	W.B.C.	F.	NF.	MM.	M.	E.	B.	Lym.	Mon.	S. I.	D. I. %
74	3.70	21.3	84	16	..	..	..	..	..	..	N	G 98
		18.0	54	28	..	..	..	..	14	4	M	G 100
82	4.05	20.8	62	20	..	..	..	..	10	8	M	G 95
		15.1	75	17	1	..	..	..	7	..	M	G 95
		17.9	28	56	2	1	..	..	12	1	G	G 100
87	4.42	19.4	58	32	..	..	..	..	8	2	S	G 100

F.–Filamented neutrophils; NF.–Non-filamented neutrophils; MM.–Metamyelocytes; M.–Myelocytes; E.–Eosinophils; B.–Basophils; S. I.–Schilling Index; D. I.–Degenerative Index.

GROUP II—20 cases (33⅓%). Cases in which the Degenerative and Schilling Indices were equal in merit; both at all times during the clinical course reflected the true state of the patient's illness.

1. *Illustrative Case.* L. R., negro male, aged 41, was admitted to the service of Dr. A. I. Rubenstone on May 11, 1935, desperately ill, septic and irrational, acidotic and dehydrated, temperature 104° F., pulse 120 and respirations 40 per minute. He had been well until 2 days before admission when dyspnea, fever, cyanosis, and hemoptysis occurred suddenly. There were signs of bilateral confluent lobular pneumonia. Urine was scanty, contained numerous casts, blood urea nitrogen was 68 mg., creatinin 2.8 mg., alkali reserve 52 volumes %, Wassermann Test positive. Sputum was negative for tubercle bacilli and positive for Pneumococcus Group IV. Spinal fluid examination yielded negative findings. Within 48 hours he developed areas of redness with cellulitis over arms and legs diagnosed erysipelas, and the blood culture taken on admission was now reported positive for hemolytic streptococcus. He remained septic, temperature ranged from 102° to

TABLE 1.—DATA OF GROUP I.

Case No.	Name.	Age (yrs.).	Diagnosis.	Number of examinations.	Clinical course.	Total leukocyte range (1000)/c.mm.	Comparative findings	Findings at most critical period of illness.
2	M. A.	3	Acute appendicitis Lobular pneumonia	6	Critically ill Septic course Temp. 102–105, expired	15.1 25.9	S. I. 0N-2M-3S-1G D. I. 0N-0M-0S-6G	L. 23,200 D. I. 97% (G) S. I. 56F-40NF-1MM-1M (G)
3	I. R.	47	Lobar pneumonia	3	Critical; temp. 104, expired	18.7 17.5	S. I. 0N-3M D. I. 0N-1M-1S-1G	L. 17,500 D. I. 63% (S) S. I. 57F-27NF (M)
4	B. F.	2	Lobar pneumonia Mastoiditis Lateral sinus thrombosis	27	Septic, toxic course; temp range 100–105	18.5 16.2	S. I. 17N-6M-2S-2G D. I. 11N-5M-9S-2G	L. 15,100 D. I. 71% (G) S. I. 32F-28NF (M)
5	A. H.	40	Lobar pneumonia	4	Toxic; sustained temp. 104	17.9 10.9	S. I. 2N-1M-0S-1G D. I. 0N-1M-0S-3G	L. 13,900 D. I. 73% (G) S. I. 45F-31NF-1MM (S)
6	M. M.	33	Lobar pneumonia	5	Toxic; sustained temp. 105	21.4 19.4	S. I. 1N-4M D. I. 1N-1M-3S	L. 21,200 D. I. 67% (S) S. I. 58F-28NF (M)
7	I. H.	17	Lobular pneumonia	7	Toxic; temp. 103	23.9 10.3	S. I. 5N-1M-1S D. I. 3N-1M-2S-1G	L. 23,900 D. I. 85% (G) S. I. 53F-41NF (G)
8	I. B.	45	Lobar pneumonia	5	Toxic; sustained temp. 105	26.0 9.1	S. I. 3N-1M-0S-1G D. I. 1N-1M-0S-3G	L. 26,000 D. I. 100% (G) S. I. 67F-24NF-5MM-2M (S)
9	J. W.	1	Lobular pneumonia	14	Septic, temp. 100–105 daily	24.6 10.7	S. I. 11N-3M D. I. 3N-5M-3S-3G	L. 10,700 D. I. 64% (S) S. I. 50F- 8NF-1MM (N)
10	F. B.	37	Lobular pneumonia	9	Toxic, septic; temp. 100–103	18.3 6.4	S. I. 4N-2M-1S-2G D. I. 1N-3M-2S-3G	L. 16,400 D. I. 95% (G) S. I. 49F-37NF-4MM (G)
11	E. C.	28	Lobar pneumonia	8	Toxic; sustained temp. 104	20.8 9.4	S. I. 2N-4M-1S-1G D. I. 2N-0M-0S-6G	L. 11,400 D. I. 100% (G) S. I. 62F-28NF-(M)
12	S. S.	7	Massive suppuration and cellulitis of thigh	7	Septic, temp. 100–104 daily	20.6 12.1	S. I. 1N-3M-1S-2G D. I. 0N-1M-3S-3G	L. 20,600 D. I. 80% (G) S. I. 32F-50NF (G)
13	F. S.	35	Pelvic peritonitis	11	Septic, temp. 102	21.2 11.4	S. I. 7N-3M-1S D. I. 4N-2M-5S	L. 21,200 D. I. 56% (S) S. I. 60F-22NF (M)
14	E. M.	5	Retropharyngeal abscess	9	Septic, temp. 104 daily	24.8 7.5	S. I. 6N-3M D. I. 3N-6M	L. 14,200 D. I. 40% (M) S. I. 49F-16NF (N)
15	B. S.	19	Purulent perinephritis	6	Toxic, septic; temp. 103	29.7 16.2	S. I. 4N-2M D. I. 0N-4M-1S-1G	L. 18,700 D. I. 86% (G) S. I. 70F-10NF (N)
16	A. H.	55	Staphylococcic septicopyemia	9	Critical, septic, temp. 100-105 daily expired.	16.2 36.4	S. I. 0N-6M-2S-1G D. I. 0N-1M-3S-5G	L. 16,100 D. I. 85% (G) S. I. 38F-52NF-1MM (G)
17	T. T.	26	Erysipelas, streptococcemia	8	Critical, septic, temp. 99–105 daily	15.2 10.2	S. I. 3N-5M D. I. 3N-1M-4S	L. 13,900 D. I. 77% (G) S. I. 58F-15NF (N)
18	A. H.	34	Infected pulmonary infarction secondary to pelvic cellulitis	6	Septic, toxic temp. 99–104	17.5 8.1	S. I. 3N-3M D. I. 2N-0M-4S	L. 17,500 D. I. 52% (S) S. I. 59F-26NF (M)
19	E. B.	26	Lobar pneumonia	4	Toxic, temp. 104	18.3 12.8	S. I. 0N-1M-2S-1G D. I. 0N-0M-3S-1G	L. 17,900 D. I. 90% (G) S. I. 59F-34NF-1MM (S)
20	J. R.	22	Lobar pneumonia	8	Toxic, temp. 102	19.2 7.6	S. I. 3N-3M-1S-1G D. I. 1N-1M-4S-2G	L. 19,200 D. I. 68% (S) S. I. 42F-54NF-1M (G)
21	E. D.	27	Metritis following Cesarean section	6	Toxic, temp. 99–102 daily	20.3 12.8	S. I. 3N-2M-1S D. I. 0N-3M-1S-2G	L. 18,500 D. I. 63% (S) S. I. 59F-25NF-1MM (M)
22	J. C.	8	Mastoiditis	9	Toxic, temp. 101–105 daily	21.4 9.8	S. I. 5N-3M-1S D. I. 1N-0M-7S-1G	L. 21,400 D. I. 67% (S) S. I. 40F-31NF (S)
23	E. S.	11	Mastoiditis	13	Toxic, temp. 100–105 daily	27.4 14.8	S. I. 7N-4M-2S D. I. 2N-5M-2S-2G	L. 21,100 D. I. 57% (S) S. I. 50F-22NF (M)
24	J. B.	2	Massive infection secondary to multiple body burns	7	Toxic, septic; temp. 100–106	30.0 8.4	S. I. 4N-3M D. I. 1N-0M-3S-3G	L. 12,1 D. I. 90% (G) S. I. 54F-28NF (M)
25	C. F.	26	Pelvic peritonitis	14	Septic, toxic; temp. 99–102	26.2 12.1	S. I. 5N-9M D. I. 0N-0M-1S-13G	L. 20,8 D. I. 94% (G) S. I. 68F-18NF (M)
26	J. L.	8	Lobular pneumonia, empyema, otitis media	23	Toxic, septic; temp. 101–105	27.9 10.4	S. I. 9N-8M-2S-4G D. I. 1N-3M-7S-12G	L. 23,900 D. I. 100% (G) S. I. 45F-40NF-4MM (G)
27	S. L.	10	Staphylococcic septicopyemia	9	Critical, septic; temp. 104–106, expired	14.6 22.2	S. I. 1N-2M-3S-3G D. I. 1N-1M-1S-6G	L. 20,200 D. I. 100% (G) S. I. 58F-28NF-0MM-4M (S)
28	L. L.	37	Lobular pneumonia	6	Toxic, septic; temp. 102–104	16.6 9.7	S. I. 2N-3M-1S D. I. 1N-3M-0S-2G	L. 14,800 D. I. 81% (G) S. I. 62F-26NF (M)
29	W. M.	4	Lobular pneumonia, mastoiditis	7	Septic, toxic; temp. 100–105	53.2 11.4	S. I. 4N-1M-1S-1G D. I. 0N-0M-4S-3G	L. 31,400 D. I. 90% (G) S. I. 38F-42NF-2MM (G)

105° F., and in spite of antistreptococcic serum, repeated blood transfusions, chemotherapy, and supportive measures he expired 5½ days after admission. The blood examinations done during his period of hospitalization are as follows:

Hb. %	R. B. C. in millions.	W. B. C.	F.	NF.	MM.	M.	E.	B.	Lym.	Mon.	S. I.	D. I.	%
90	4.50	21.4	39	50	4	..	..	..	7	..	G	G	80
83	4.22	21.9	38	40	5	1	..	..	13	3	G	G	83
86	4.12	16.6	23	45	11	1	..	..	16	4	G	G	87

TABLE 2.—DATA OF GROUP II.

Case No.	Name.	Age (yrs.).	Diagnosis.	Number of examinations.	Clinical course.	Total leukocyte range 1000/c.mm.	Comparative findings.	Findings at most critical period of illness.
2	L. G.	55	Lobular pneumonia	5	Septic, toxic; temp. 102; expired	27.1 28.9	S. I. 0N-1M-3S-1G D. I. 0N-1M-2S-2G	L. 20,600 D. I. 77% (G) S. I. 40F-38NF-2MM-1M (G)
3	H. N.	21	Lobar pneumonia	9	Toxic; sustained temp. 104	11.9 9.1	S. I. 3N-2M-3S-1G D. I. 2N-2M-4S-1G	L. 8,400 D. I. 90% (G) S. I. 42F-34NF (S)
4	M. R.	51	Lobular pneumonia; toxic hepatitis	13	Septic, toxic; temp. 103	25.6 8.5	S. I. 5N-3M-4S-1G D. I. 4N-5M-2S-2G	L. 12,800 D. I. 72% (G) S. I. 45F-31NF-1MM (S)
5	J. H.	40	Lobular pneumonia	5	Septic, toxic; sustained temp. 105	60.4 7.6	S. I. 2N-0M-1S-2G D. I. 1N-0M-1S-3G	L. 60,400 D. I. 100% (G) S. I. 38F-34NF-9MM-9M (G)
6	C. H.	46	Lobar pneumonia empyema	8	Toxic; temp. 103–105	22.5 13.5	S. I. 4N-4M D. I. 5N-1M-2S	L. 22,500 D. I. 58% (S) S. I. 68F-21NF (M)
7	I. F.	42	Lobular pneumonia	3	Toxic; temp. 104	9.2 8.1	S. I. 1N-1M-1S D. I. 1N-1M-1S	L. 9,200 D. I. 49% (S) S. I. 54F-26NF (M)
8	J. G.	3	Lobular pneumonia; mastoiditis	5	Septic, toxic, temp. 105–106	42.4 9.8	S. I. 2N-0M-2S-1G D. I. 2N-0M-1S-2G	L. 42,400 D. I. 71% (G) S. I. 62F-22NF (M)
9	S. S.	3	Lobar pneumonia	5	Toxic; temp. 105	27.4 11.3	S. I. 0N-3M-0S-2G D. I. 0N-1M-1S-3G	L. 10,200 D. I. 90% (G) S. I. 26F-18NF-4MM-10M (S)
10	I. E.	50	Lobular pneumonia; toxic psychosis	6	Septic; temp. 99–103	5.4 9.7	S. I. 5N-1M D. I. 4N-1M-1S	L. 9,700 D. I. 48% (M) S. I. 44F-21NF (M)
11	M. S.	38	Lobular pneumonia	9	Toxic; temp. 105	19.3 12.2	S. I. 4N-4M-1S D. I. 5N-2M-2S	L. 15,300 D. I. 82% (G) S. I. 59F-15NF (N)
12	M. S.	23	Lobar pneumonia	7	Toxic; temp. 103; sustained	28.0 12.9	S. I. 2N-3M-2S D. I. 3N-2M-2S	L. 15,000 D. I. 51% (S) S. I. 59F-21NF- (M)
13	H. S.	19	Staphylococcic septicopyemia	24	Critical; septic; temp. 100–102; expired	17.4 24.9	S. I. 0N-4M-13S-7G D. I. 0N-0M-9S-15G	L. 17,500 D. I. 100% (G) S. I. 32F-59NF-7MM-1M (G)
14	C. S.	45	Osteomyelitis	7	Toxic, septic; temp. 103	27.4 10.4	S. I. 1N-4M-2S D. I. 1N-2M-2S-2G	L. 27,400 D. I. 83% (G) S. I. 68F-26NF (M)
15	S. L.	27	Pelvic peritonitis	19	Septic; temp. 102	20.0 8.5	S. I. 8N-4M-0S-7G D. I. 3N-4M-6S-6G	L. 15,500 D. I. 71% (G) S. I. 32F-50NF-1MM (G)
16	A. W.	14	Generalized peritonitis secondary to ruptured appendicitis	14	Toxic, septic; temp. 99–104	22.7 6.3	S. I. 5N-4M-3S-2G D. I. 4N-4M-4S-2G	L. 16,700 D. I. 74% (G) S. I. 50F-31NF-1MM (S)
17	E. K.	47	Generalized peritonitis secondary to ruptured appendicitis; lobular pneumonia	6	Septic, toxic; temp. 100–104	20.8 10.4	S. I. 0N-4M-1S-1G D. I. 1N-3M-0S-2G	L. 20,800 D. I. 86% (G) S. I. 59F-22NF (M)
18	M. F.	4	Generalized peritonitis secondary to ruptured appendicitis	7	Septic, toxic; temp. 102	23.2 11.3	S. I. 0N-1M-2S-4G D. I. 0N-1M-1S-5G	L. 14,800 D. I. 96% (G) S. I. 39F-42NF-2MM-1M (G)
19	H. F.	2	Mastoiditis	5	Toxic; temp. 102	17.1 10.2	S. I. 3N-2M D. I. 3N-1M-1S	L. 17,100 D. I. 61% (S) S. I. 52F-21NF (M)
20	M. B.	28	Suppurative metritis	4	Toxic; temp. 102	18.1 12.4	S. I. 0N-3M-0S-1G D. I. 0N-2M-2S-0G	L. 12,400 D. I. 65% (S) S. I. 52F-21NF (M)

GROUP III—7 cases (11.7%). Cases in which the Degenerative Index alone was positive and reflected the clinical state of the patient, the Schilling Index being of no value.

1. *Illustrative Case.* L. B., female child, aged 5 years, admitted to the service of Dr. B. Lipschutz in August, 1933, in state of severe shock due to extensive body burns involving an area covering the entire anterior surface of the body reaching from the chin and face to the symphysis pubis, from posterior axillary line of one side to posterior axillary line of the other. There were also additional burns of back and extremities. She was treated locally with tannic acid solution, and generally with repeated blood transfusions, venoclysis, and supportive measures. Over half the body surface was involved with second and third degree burns; infection set in with toxemia and sepsis, the child became weaker and more debilitated, temperature fluctuated from 100°–105° F. daily, and she expired in September, 1934, more than 1 year after admission. Blood examinations made at weekly intervals during her most septic state prior to exitus are as follows:

Hb. %	R.B.C. in millions.	W.B.C.	F.	NF.	MM.	M.	E.	B.	Lym.	Mon.	S. I.	D. I. %
81	4.00	21.7	38	37	2	1	..	..	21	1	S	G 75
		21.5	42	32	..	1	..	3	21	1	S	G 88
		20.8	55	19	1	..	..	..	18	7	M	G 84
78	3.94	18.4	59	21	..	..	..	..	15	5	M	G 79
		26.5	63	16	..	..	..	..	19	2	N	G 87
		14.4	45	28	..	..	..	..	21	6	M	G 100
77	3.75	33.4	64	26	..	..	..	..	9	1	M	G 91

TABLE 3.—DATA OF GROUP III.

Case No.	Name.	Age (yrs.).	Diagnosis.	Number of examinations.	Clinical course.	Total leukocyte range 1000/c.mm.	Comparative findings.	Findings at most critical period of illness.
2	L. G.	22	Lobar pneumonia; pneumococcemia; empyema	8	Toxic, septic; temp. 101–103	20.2 10.4	S. I. 7N-1M D. I. 0N-0M-1S-7G	L. 20,200 D. I. 76% (G) S. I. 44F-21NF (M)
3	A. D.	5	Lobular pneumonia	4	Critical; toxic; expired; temp. 104	13.9 21.2	S. I. 3N-1M D. I. 0N-0M-0S-4G	L. 16,900 D. I. 87% (G) S. I. 46F-21NF (M)
4	M. B.	4	Lobular pneumonia; mastoiditis	5	Toxic, septic; temp. 99–103	21.4 14.5	S. I. 5N D. I. 0N-1M-4S	L. 21,400 D. I. 75% (G) S. I. 32F-14NF (N)
5	M. M.	27	Septic metritis; pelvic peritonitis	9	Toxic, septic; temp. 100–105	26.5 9.1	S. I. 8N-1M D. I. 4N-3M-2S	L. 25,600 D. I. 40% (M) S. I. 72F-16NF (N)
6	A. S.	31	Septic abortion; peritonitis	6	Toxic, septic; temp. 100–106	14.9 8.1	S. I. 5N-1M D. I. 1N-4M-1S	L. 14,200 D. I. 60% (S) S. I. 71F-12NF (N)
7	F. J.	22	Retropharyngeal abscess	5	Toxic; temp. 100–103	21.4 9.8	S. I. 5N D. I. 2N-2M-1S	L. 12,600 D. I. 64% (S) S. I. 47F-12NF (N)

GROUP IV—3 cases (5%). Cases in which both the Degenerative and the Schilling Indices were positive, but in which the Schilling Index at all times was more informative, reflecting the clinical state with a greater degree of accuracy than the Degenerative Index.

1. *Illustrative Case.* W. C., sthenic, white male, aged 44, referred by Dr. J. Levy, was admitted to the hospital on April 28, 1935, acutely ill, complaining of cough, pain in the chest, and expectoration of 1 day's duration. Temperature was 103° F. Consolidation of the left upper lobe was diagnosed and confirmed by Roentgen ray examination. Blood chemistry, culture, and serology were normal. Sputum examination yielded Pneumococcus Group IV and was negative for tubercle bacillus. Temperature ranged from 101° to 105° F., then dropped to normal on the 7th day, rose to 100° for a few days, reached normal and remained there. Although he presented the usual toxicity for lobar pneumonia, his clinical course was favorable throughout, and he was discharged 3 weeks after admission as cured. Blood examinations taken periodically during the severe stage of his illness disclosed the following:

Hb. %	R.B.C. in millions.	W.B.C.	F.	NF.	MM.	M.	E.	B.	Lym.	Mon.	S. I.	D. I.	%
100	5.17	29.6	42	52	4	..	..	..	2	..	G	N	20
		28.2	42	47	2	..	..	..	8	1	G	S	41
		15.3	41	37	4	..	2	..	16	..	G	S	57
95	5.10	15.1	56	14	..	1	2	..	22	5	N	S	46
		31.4	30	50	4	..	..	..	14	2	G	S	67
		32.0	35	53	3	1	..	..	8	..	G	S	60
		14.6	39	21	4	2	3	..	27	4	M	S	45
105	5.20	10.4	36	20	2	..	4	..	32	6	M	N	18
		10.2	49	5	1	..	..	..	40	5	N	N	7

TABLE 4.—DATA OF GROUP IV.

Case No.	Name.	Age (yrs.).	Diagnosis.	Number of examinations.	Clinical course.	Total leukocyte range 1000/c.mm.	Comparative findings.	Findings at most critical period of illness.
2	J. A.	55	Lobular pneumonia	2	Septic; critical; temp. 104; expired	18.9 15.4	S. I. 0N-0M-0S-2G D. I. 0N-0M-2S-0G	L. 15,500 D. I. 65% (S) S. I. 15F-55NF-14MM-2M (G)
3	I. K.	6	Lobar pneumonia mastoiditis; empyema	4	Septic; critical; temp. 105–107; expired	16.0 6.2	S. I. 0N-0M-0S-4G D. I. 1N-1M-1S-1G	L. 6,200 D. I. 91% (G) S. I. 17F-39NF-1MM-1M (G)

GROUP V—1 case (1.7%). Cases in which the Schilling Index alone was positive and reflected the clinical state of the patient, the Degenerative Index being practically of no value.

1. *Illustrative Case.* S. A., female, aged 25, admitted to the service of Dr. Moses Behrend on February 23, 1934, for nausea, vomiting, fever, and pain in right lower abdomen of 5 days' duration. Temperature was 101° F. Patient was toxic and dehydrated, urine showed +2 acetone. Diagnosis of peritonitis secondary to ruptured appendicitis was made, the abdomen opened, gangrenous ruptured appendix removed, and the peritoneal cavity drained. The postoperative course was stormy, complicated by ileus and the development of a pelvic abscess necessitating rectal incision for drainage. Temperature ranged between 101° and 102° F. daily. Several blood transfusions were given. Finally drainage decreased, clinical condition improved, temperature reached normal on the 28th day, and she was discharged cured

on the 35th day following admission. Blood examinations during the course of her septic state are as follows:

Hb. %	R.B.C. in millions.	W.B.C.	F.	NF.	MM.	M.	E.	B.	Lym.	Mon.	S. I.	D. I.	%
85	4.45	25.9	70	18	..	..	..	..	10	2	M	N	0
		21.2	58	28	1	1	..	..	10	2	M	N	10
		20.4	59	28	..	..	..	1	10	2	M	S	50
		25.8	45	38	1	2	..	..	13	1	G	N	17
81	4.20	19.3	44	32	..	..	..	..	22	2	S	N	0
		10.9	53	30	..	..	..	..	15	2	M	N	12
		15.0	56	8	..	..	..	..	32	4	N	N	6
88	4.50	11.8	68	12	..	..	2		16	2	N	N	0

The following table represents the compared Indices of the entire series of the 60 cases at the most critical period of the patients' illnesses:

	Normal.	Moderate.	Severe.	Grave.
Schilling Index	9	23	11	17
Degenerative Index	1	3	18	38

Discussion. From this study it would appear that in severe infections, serial estimations of the degenerative cytoplasmic changes in neutrophils, as expressed by the Degenerative Index, are a more reliable and accurate guide of the severity and prognosis of the illness than estimations of nuclear changes, as expressed by the Schilling Index. This is shown in diseases presenting both nuclear and cytoplasmic changes namely, the severe toxic states encountered in septicemia, bacteremia, pneumonia, peritonitis, osteomyelitis, and severe mastoiditis. In the advanced stages of infection the polymorphonuclear neutrophils show the greatest degree of cytoplasmic and nuclear changes, and therefore, such disease states offer the best basis for the comparison of the values of these two findings. We have shown in our previous work that mild infectious states, as rheumatic fever, arthritis, tuberculosis, etc., usually do not present cytoplasmic degenerative changes whereas the Schilling shift may or may not be marked. Such diseases, therefore, do not offer themselves for a comparative study. Hence it is evident that the results of our study are applicable only to severe infectious states and may not hold for relatively milder disease states.

In general, the results of this study may be summarized as follows: In these extremely septic states, while the Schilling count was of value and a good index of the patient's clinical condition, it was not as valuable or as accurate and reliable as the Degenerative Index in the majority of cases. In 20 cases of the 60 studied (Group II) both the Degenerative and Schilling Indices were equally valuable. Of the remaining 40 cases, in 36 (90%) (Groups I and III), the Degenerative Index was superior to the Schilling Index; whereas in the other 4 cases (10%) (Groups IV and V), the Schilling Index was superior to the Degenerative Index. We also noted in the course of our serial examinations that the degenerative cytoplasmic changes

appeared earlier in the illness and persisted longer throughout the course than did the corresponding nuclear changes. Again, at the height of the diseases studied, during the most critical days of the patients' illnesses, a single examination comparing the two tests found the Degenerative Index to be superior; it denoted 38 grave states as compared to 17 by the Schilling Index, and 18 severe states as compared to 11 by the Schilling Index.

Conclusions. 1. Sixty cases of severe infectious diseases have been studied to compare the relative value clinically of the degenerative cytoplasmic changes (Degenerative Index) and the nuclear changes (Schilling Index) in polymorphonuclear neutrophils.

2. In 20 of the 60 cases studied both the Degenerative Index and Schilling Index proved to be of equal value.

3. Of the remaining 40 cases, in 36 (90%) the Degenerative Index was superior to the Schilling Index. In only 4 of these 40 cases (10%) was the Schilling Index superior to the Degenerative Index.

4. This series showed that at the height of the illness the Degenerative Index more accurately reflected the existing clinical state and the subsequent course.

5. Degenerative cytoplasmic changes appeared earlier, and persisted longer than did the corresponding nuclear changes during the critical stages of the illnesses studied.

6. It is important to note how valuable both tests proved to be, and that though the Degenerative Index proved to be superior in the majority of cases, the Schilling Index again showed itself to be a very valuable procedure.

7. From this study it is again evident that no hemogram in severe infection is complete without determination of the Degenerative Index.

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CHRONIC CONSTRICTIVE PERICARDITIS, ELECTROCARDIOGRAPHIC AND CLINICAL STUDIES.

By E. H. Cushing, M.D.,

SENIOR CLINICAL INSTRUCTOR OF MEDICINE, WESTERN RESERVE UNIVERSITY AND LAKESIDE HOSPITAL,

AND

H. S. Feil, M.D.,

ASSISTANT CLINICAL PROFESSOR OF MEDICINE, WESTERN RESERVE UNIVERSITY AND LAKESIDE HOSPITAL, CLEVELAND, OHIO.

(From the Department of Medicine.)

Chronic constrictive pericarditis has been known as a clinical entity since the early descriptions by Widenmann[1] and Kussmaul.[2] Pick[3] described the condition in the following words: "There is a symptom complex characterized by circulatory disturbances, enlarged liver and ascites, caused by latent pericarditis." This symptom complex has been known by his name for many years. The clinical features are characterized by high venous pressure, lowered arterial pressure with a low pulse pressure, pulsus paradoxus (first described by Widenmann[1]), ascites and enlarged liver. There is little cardiac enlargement. Broadbent's sign and systolic retraction of the lower sternum or the left lower chest are rarely observed. The electrocardiogram may be an additional aid in establishing the diagnosis of this condition. Eleven cases of constrictive pericarditis with low voltage curves have been reported: Sprague and White,[4] 1; Willius and Killins,[5] 2; Turner,[6] 1; Waldorp,[7] 1; Burwell and Strayhorn,[8] 1; and White[9] reports 5 cases with low voltage and 10 with abnormalities in the *T* waves.

The following observations were made upon 11 patients with the clinical diagnosis of chronic increased intrapericardial pressure. Pericardectomy was performed on all of these patients by Dr. C. S. Beck,[10] who has reported case histories of 6 of the patients referred to in this paper. Microscopic examination of the resected pericardium in all instances showed the parietal and visceral layers to be fused and indistinguishable, with densely fibrous and hyalinized tissue which was poorly vascularized. Occasional small collections of lymphocytes were observed. Some of the cases showed focal

TABLE 1.—VOLTAGE OF ELECTROCARDIOGRAMS OF 11 CASES.

Date.	*P*, mm.	*Q*, mm.	*R*, mm.	*S*, mm.	*T*, mm.	Axis shift.
Case 1.	F. L., ♂, aged 13 yrs.					
9/20/29	+1.5(II)†	−1(III)	+5.5(III)	−0.75(II)	Isoelectric	0
11/21/29	Pericardectomy					
12/24/29	+1.75(II)	−3(III)	+12(II)	−3(I)	Iso.(I) −1(II) −5(III)	0
3/19/30	+1.5(II)	−4(III)	+12.5(II)	−4.5(I)	+1(I) −0.5(II) −1.5(III)	0
3/ 3/34	+2(II)	−3.5(II)	+25(II)	−4.5(I)	+1.5(I) +2.5(II) −1.5(III)	0
Case 2.	J. V., ♂, aged 30 yrs.					
4/17 31	+1.5(II)	−1(III)	+5.5(II)	−1(I)	−0.5(I) −0.5(II)	
8/ 8/31	Pericardectomy				Iso.(III)	
Case 3.	M. F., ♀, aged 23 yrs.					
11/20/31	+1.75(I, II)	...	+5(II)	−0.5(III)	Isoelectric 0.5(II)	0
11/25/31	Pericardectomy	...	...	...	Iso.(III)	
Case 4.	I. M., ♀, aged 32 yrs.					
1/25/33	+1.5(I)	...	+3(II)	−2.25(II)	+1(I) +0.5(II) −1(III)	0
2/2/33	Pericardectomy					
4/13/33	+1.5(I)	...	+2(II)	−1.25(II)	+1(I) Iso.(II) −1(III)	
4/13/34	+1.5(I)	−0.5(III)	+4(I)	−2(I)	+1.5(I) +0.5(II) −1.5(III)	Slight.
8/22/35	+1.5(I)	−0.5(III)	+3(I)	−2(I)	+1.5(I) +0.5(II) −1.5(III)	0
Case 5.	G. R., ♂, aged 28 yrs.					
7/19/33	+1(I)	−0.5(I)	+5(II)	−1.5(I)	−0.5(I) −1.5(II) −1(III)	Slight.
7/31/33	Pericardectomy					
8/11/33	+1(I, II)	−0.25(I)	+4(II)	−2.5(II)	+0.75(I) −1(II) −0.5(III)	
4/14/34	+1.5(I)	−0.5(I)	+2.5(II)	−2(II)	−0.5(I) −1(II) −0.5(III)	0
8/23/34	+1.5(I)	−1(I)	+4.5(III)	−2(I)	Diph. ±0.5 −1(II) −0.5(III)	
Case 6.	G. B., ♂, aged 25 yrs.					
3/12/34	Auricular fibrillation	...	+7(II)	−3(II)	−0.5(I) −1(II) −0.5(III)	0
4/ 7/34	Auricular fibrillation	...	+5(II)	−3(II)	−1(I)	
4/ 7/34	Pericardectomy				−1(II) Iso.(III)	
6/21/34	Auricular fibrillation	...	+6(II)	−2(II)	Iso.(I) Iso.(II) Iso.(III)	
6/24/35	Auricular fibrillation	...	+9(II)	−2.5(II)	+1.0(I) Iso.(II) −1.5(III)	Definite.
Case 7.	M. Z., ♀, aged 37 yrs.					
5/17/34	Auricular fibrillation Pericardectomy	...	+4.5(II)	−0.5(I)	−0.5(I) −0.5(II) Iso.(III)	Slight.
Case 8.	E. C., ♂, aged 15 yrs.					
8/ 3/34	+1.5(II) Pericardectomy	−5(IV)	+7(II)	...	+1(I) +0.5(II) −0.5(III)	0

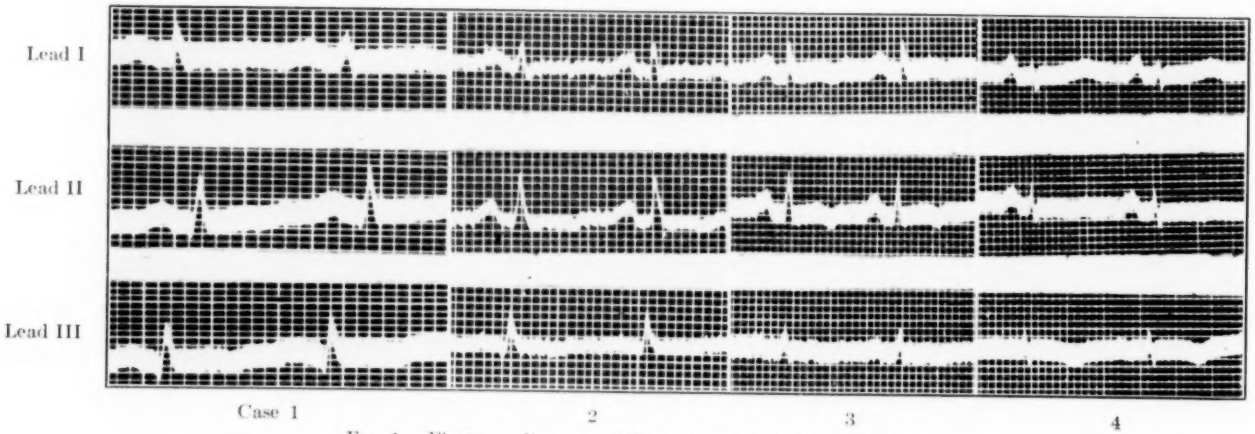

FIG. 1.—Electrocardiograms of Cases 1 to 4, before operation.

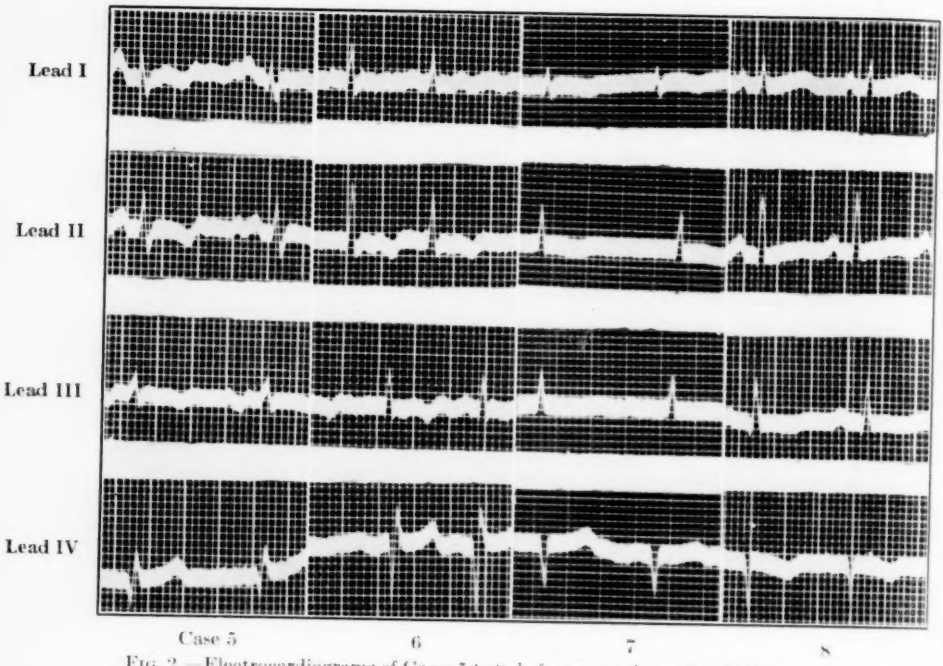

FIG. 2.—Electrocardiograms of Cases 5 to 8, before operation. Lead IV: apex—left leg.

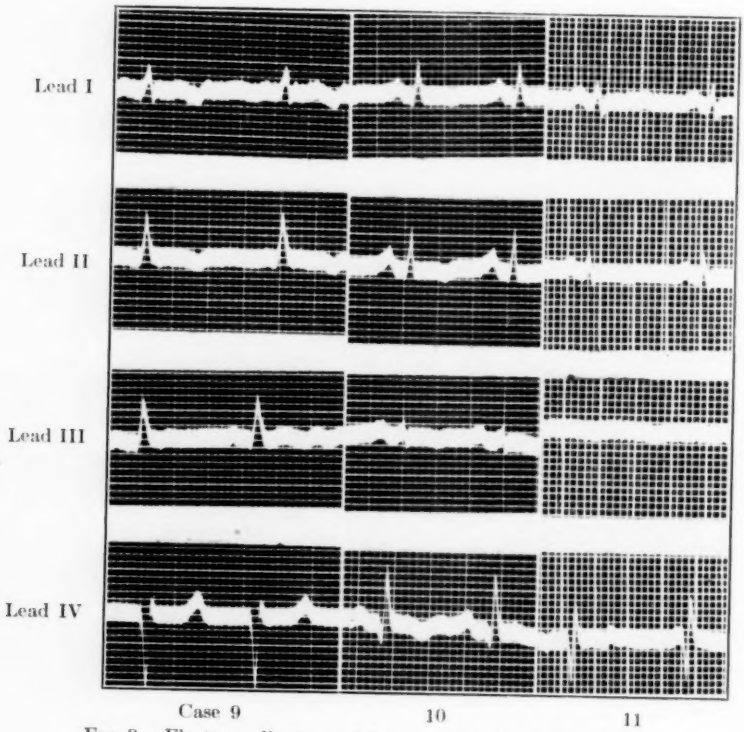

FIG. 3.—Electrocardiograms of Cases 9 to 11, before operation.

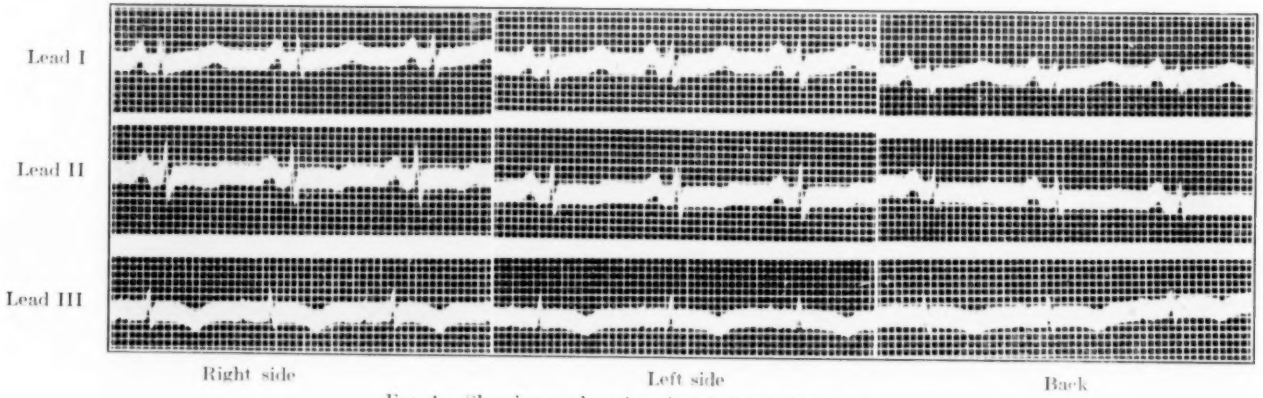

FIG. 4.—Showing unchanging electrical axis (Case 4).

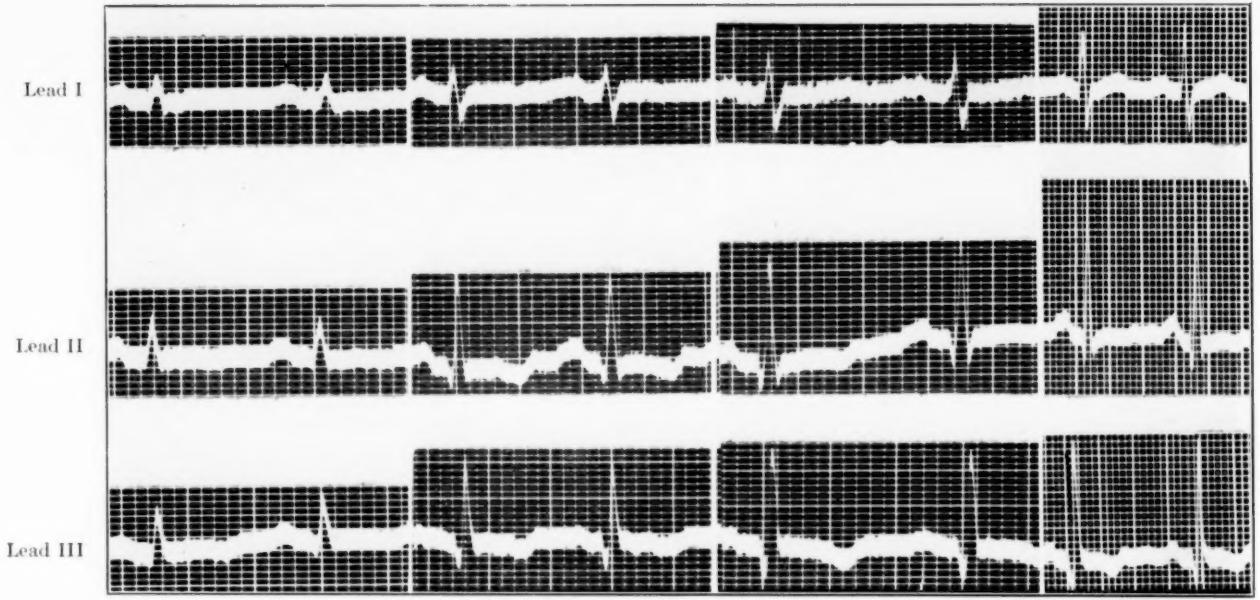

FIG. 5.—Progressive increase in voltage, following operation (Case 1).

TABLE 1.—VOLTAGE OF ELECTROCARDIOGRAMS OF 11 CASES.—*Continued.*

Date.	*P*, mm.	*Q*, mm.	*R*, mm.	*S*, mm.	*T*, mm.	Axis shift.
Case 9.	B. S., ♀, aged 57 yrs.					
2/17/33	Auricular flutter	...	+7(III)	−1.5(I)	...	Slight.
4/13/34	Auricular flutter	...	+4.25(II)	−0.5(I)	+0.5(I)	
4/17/34	Auricular fibrillation	...	+4.5(II)	...	+1(II)	
					−0.5(III)	
11/ 8/34	Auricular fibrillation	...	+5(II)	−1(I)	−0.5(I)	
					−1(II)	
					−0.5(III)	
11/10/34	Pericardectomy					
11/26/34	Auricular fibrillation	−0.5(III)	+5(II)	−1.5(I)	−0.5(I)	
					−1.25(II)	
					−0.25(III)	
12/20/34	Auricular fibrillation	−0.5(III)	+7(II)	...	−0.5(I)	
					−1(II)	
					−0.5(III)	
4/ 3/35	Auricular fibrillation	−0.5(III)	+10(III)	...	−0.5(I)	
					−1.5(II)	0
					−0.25(III)	
Case 10.	I. L., ♂, aged 30 yrs.					
10/ 3/33	+1.5(II)	...	+7(II)	...	−1(I)	
					+1.5(II)	0
					+0.5(III)	
12/ 1/34	+1.5(II)	−0.5(I)	+5(II)	−0.5(III)	+0.5(I)	
					−0.5(II)	
					−0.25(III)	
1/15/35	Pericardectomy					
1/31/35	+1.5(II)	−0.5(I)	+6(II)	...	−0.5(I)	
					−0.5(II)	0
					−0.25(III)	
12/10/35	+2.25(II)	−0.5(I)	+7(II)	−0.5(III)	−0.5(I)	0
					−1.0(II)	
					−0.5(III)	
Case 11.	V. P., ♂, aged 46 yrs.					
4/ 3/35	+1(II)	...	+2(II)	−0.5(II)	+0.5(I)	
					−0.5(II)	0
					Iso.(III)	
4/10/35	Pericardectomy					
6/25/35	+1(II)	...	+3.5(I)	−2(I)	−0.25(I)	
					−0.5(II)	0
					−0.25(III)	

† Indicates lead with highest voltage.

areas of calcification. There were no changes that could be construed as characteristic of rheumatic or tuberculous infection.

Electrocardiographic studies were made in all cases. Certain features were common to all of the records: Voltage of the *Q–R–S* complex below the usual limits of normal;* slurring of the *Q–R–S* in all leads; and *T* waves of low amplitude, either of positive or of negative sign. The presence of *P* waves of normal voltage was an interesting finding (Figs. 1, 2 and 3). In 7 of the cases, change of position did not appreciably affect the electrical axis (Fig. 4), and only changed it slightly in 3 cases. In 1 case the test was not made.

The chest lead showed a *Q* wave in all cases and in only 1 case was an *S* wave observed. The *T* wave was upright in 5 of the 7 cases.

In Table 1 are listed the electrocardiographic observations in the 11 cases.

* Significance of voltage: The normal electrocardiogram is the resultant of electrical effects originated in the heart and conducted by the body tissues to the electrodes on the extremities. The resultant maximum voltage (in any one recorded lead) is a small fraction of the total voltage in direct leads from the heart. The latter figure has a value of approximately 20 times that of the conventional electrocardiogram.

Table 2 shows the details of the chest lead which was placed in the fourth interspace just lateral to the sternum.

TABLE 2.—LEAD IV* IN 7 CASES.

Date.		*P*, mm.	*Q*, mm.	*R*, mm.	*S*, mm.	*T*, mm.
Case 5.	G. R., ♂, aged 28 yrs.					
7/19/33	.....	Isoelectric	−3.0	+4.5	...	+1.5
7/31/33	Pericardectomy					
9/23/33	.....	−0.5	−1.5	+2.0	...	+0.5
8/23/34	.....	−0.5	−2.0	+4.25	...	+1.0
Case 6.	G. B., ♂, aged 25 yrs.					
3/12/34	Auricular fibrillation	...	−8.5	+4.0	...	+2.0
4/ 7/34	Pericardectomy					
6/21/34	Auricular fibrillation	...	−6.0	+5.5	...	−1.0† +2.0†
6/24/35	Auricular fibrillation	...	−6.0	+6.5	...	−2.0
Case 7.	M. S., ♀, aged 37 yrs.					
5/17/34	Auricular fibrillation	...	−3.5	...	...	+1.0
Case 8.	E. C., ♂, aged 15 yrs.					
8/ 3/34	.....	+0.5	−5.5	...	...	−1.25
Case 9.	B. S., ♀, aged 57 yrs.					
4/13/34	Auricular flutter	...	−14.0	+2.0	...	Upright.
11/10/34	Pericardectomy					
4/ 3/35	Auricular fibrillation	...	−5.0	+24.0	−2.0	+3.5
Case 10.	I. L., ♂, aged 30 yrs.					
10/ 3/33	.....	+0.5	−13.0	+5.0	...	+3.0
12/ 1/34	.....	Diphasic ±0.5	−7.5	+1.0	...	−0.5
1/15/35	Pericardectomy					
12/10/35	.....	Diphasic	...	+1.0	−10.0	+1.5
Case 11.	V. P., ♂, aged 46 yrs.					
4/ 3/35	.....	−0.5	−5.0	+4.5	...	−2.5
4/10/35	Pericardectomy					
6/25/35	.....	−0.25	−5.5	+7.25	...	+4.0

* Lead IV. Chest electrode in fourth interspace to left of sternum. Indifferent electrode on left leg.
† Varying.

Following operation 4 cases (1, 6, 9, 11) showed an increase in voltage. There was no change in the *P* or *T* waves.

Electrocardiograms were taken during the operative procedure on 4 patients. There were surprisingly few changes to be observed.* Ventricular extrasystoles were noted in 3 of the 4 cases when the pericardium was being dissected from the heart. There was a transient change in mechanism in 3 patients, shifting pacemaker

* Kurtz, C. M., Bennett, J. M., and Shapiro, H. H., J. Am. Med. Assn., **106**, 434, 1936, report similar electrocardiographic changes during surgical anesthesia.

being noted twice and nodal rhythm once. There was slight elevation of the S–T interval in the first and second leads during operation in 2 cases, but this had disappeared by the time the procedure was completed. The details of the changes observed, the blood pressure readings and the rate are listed in Table 3:

TABLE 3.—CHANGES OBSERVED DURING OPERATION.

Case No.	Start of operation.	Mediastinum opened.	Heart bulging through pericardium.	Heart freed of pericardium.	End of operation.
Case 8 E. C.	Rate, 124–156; shifting pacemaker Blood pressure, 104/70	Rate, 142; normal mechanism Blood pressure, 115/70	... Blood pressure, 120/70	Rate, 144; rare ventricular extrasystoles; lower voltage; S and T waves sl. elevated Blood pressure, 125/70	Rate, 138; occasional ventricular extrasystoles; voltage still lower.
Case 9 B. S.	Rate, 122 Blood pressure, 120/100	Rate, 136 Blood pressure, 105/75	Rate, 136 Blood pressure, 125/80	Rate, 112 Blood pressure, 130/80	Rate, 150; very slight decrease in voltage. Blood pressure, 130/90
Case 10 I. L.	Rate, 152 Blood pressure, 123/82	Rate, 128; voltage slightly increased Blood pressure, 145/90	Rate, 136; occasional ventricular extrasystoles; shifting pacemaker Blood pressure, 115/90	Rate, 124; shifting pacemaker Blood pressure, 115/80	Rate, 136; normal mechanism. Blood pressure, 105/70
Case 11 V. P.	Rate, 96	Rate, 111; nodal rhythm	Rate, 121; nodal rhythm; ventricular extrasystoles; elevated S and T waves in Leads I and II	Rate, 116; normal mechanism; S and T_3 isoelectric; S and T waves sl. elevated; occasional ventricular extrasystoles	Rate, 98; nodal rhythm; S and T waves in Leads I and II isoelectric.

Table 4 shows in tabular form the clinical findings on the 7 cases that recovered from the operative procedure:

TABLE 4.—CIRCULATORY TESTS BEFORE AND AFTER OPERATION.

Case No.	Pre-operative.				Interval since operation.	Postoperative.			
	Blood pressure.	Venous pressure, cm.	Vital vapacity, %.	Cardiac output, %.		Blood pressure.	Venous pressure, cm.	Vital capacity, %.	Cardiac output, %.
1	90/70	35	55	...	4½ yrs.	128/78	3.5	80	−12.3
4	90/72	25	60	−42.3	14 mos.	118/72	..	81	−39.0
5	96/74	27	52	−50.4	9 "	110/70	18.0	82	−37.0
6	100/80	28	68	−28.6	14 "	112/78	17.0	..	− 3.2
9	104/90	32	58	−41.0	5 "	120/70	18.0	69	−28.0
10	105/85	35	40	−25.0	4 "	110/75	19.0	..	− 9.5
11	110/70	25	36	−36.4	2½ "	120/70	13.0	47	−17.7

Blood pressure is in millimeters of mercury. The venous pressure is in centimeters of physiologic solution of sodium chlorid. The vital capacity is in percentage of estimated normal. Cardiac output is by Grollman's acetylene method in percentage.

Dieuaide[11] noted that change in the position of patients with adhesive pericarditis from one lateral position to the other is not followed by the normal change in the electrical axis of the heart, seen most prominently in Leads I and III of the electrocardiogram. In normal individuals, there is usually a significant shift of the electrical axis; and in patients with rheumatic heart disease, there is usually a considerable shift. In Dieuaide's series, 12 patients came to necropsy. These included 8 with clinical signs suggestive of adhesive pericarditis, 4 of whom had a relatively fixed electrical axis, and all showed lesions of the pericardium and of the mediastinum. Pathologic findings in the pericardium and mediastinum were lacking in the other autopsied cases. In the 3 patients with fixation of the electrical axis in Dieuaide's series (Cases 5, 6 and 7), the maximum voltage of *Q–R–S* was 22, 14 and 18 mm., respectively; *i. e.*, voltage above the normal figure. The first of these patients had syphilitic heart disease and the other 2 rheumatic heart disease. The large voltage in these cases agrees with our findings in rheumatic heart disease and serves to differentiate the latter condition from non-rheumatic adhesive mediastinopericarditis.

Electrocardiograms from 100 cases of rheumatic heart disease at Lakeside Hospital were reviewed, of which cases 21 came to necropsy. Table 5 is a summary of the findings in these cases.

TABLE 5.—ELECTROCARDIOGRAPHIC VOLTAGE IN 100 CASES OF RHEUMATIC HEART DISEASE.

	No. of cases.	Age range.	Maximum voltage range.	Average maximum voltage.*
Cases with active infection (rheumatic or subacute bacterial)	31	14–39	7–43	15.8
Cases with congestive failure	30	13–63	4.5–28	12.5
Cases with heart disease an incidental finding	39	7–66	7–31	15.6
Average of all cases	..	..	..	14.6

* In Lewis'[12] series of 52 normal medical students, the variations in the height of the largest wave of *Q–R–S* were from 5.5 to 16.5 mm., with an average of 11 mm. In Pardee's[13] series of 26 normal college students, the voltage varied from 8 to 23.5 mm. Pardee concluded that from these 78 normal records, the minimum value should be 7 mm. and the maximum value 17 mm. In Hallaran and Shipley's[14] series of 200 normal individuals between 20 and 35 years of age, the average voltage for men was 12.4 mm., varying from 19.2 to 5.8 mm. (3 men had voltage below 7 mm; their voltage was 6.7, 5.8 and 5.8 mm.). The 100 women had an average voltage of 10.8 mm., varying between 19.7 and 3.6 mm. (There were 11 women with voltages below 7 mm. and 4 below 6 mm. The lowest voltage was in a woman who had a basal metabolic rate of −14.)

This increase in voltage of the *Q–R–S* complex is found in the cases of active infection as well as in the group without evidence of active infection or of congestive failure. In the cases of congestive failure, the voltage range was from 4.5 to 28 mm., with an average voltage of 12.5 mm., slightly less than the average in the remaining cases. In only 1 case was low voltage found (4.5 mm.) and the

necropsy of this case revealed extensive mediastinopericardial adhesions and severe myocardial scarring. In the 100 cases the voltage was 7 mm. or less in 6 instances. Of these, 3 had congestive failure, 1 subacute bacterial endocarditis, 1 acute rheumatic fever, and in 1 case the cardiac lesion was incidental.

The low amplitude of the *Q–R–S* complex and of the *T* waves in these cases of adhesive mediastinopericarditis could be explained by severe myocardial damage or by change in the tissues immediately surrounding the heart (dense adhesions, hydropericardium, hydrothorax and ascites). Severe myocardial damage as a cause of low amplitude is difficult to reconcile with the practically complete clinical recovery in Case 1 (Fig. 5), the increased voltage in 4 of the cases recovering from operation, and the absence of myocardial involvement as shown by histologic examination in Cases 3, 5 and 7. The absence of low voltage in curves recorded from cases of rheumatic heart disease with advanced congestive failure suggests that changes in conduction remote from the heart do not entirely explain the low voltage. Conditions immediately surrounding the heart, such as fluid or dense adhesions, do reduce the amplitude of the electrocardiogram. This reduction in voltage was seen in the experimentally produced pericardial effusion of Katz, Scott and Feil.[15] Likewise Wilson,[16] in his experimental work, showed that "any increase in the conductivity of the body tissues, particularly of those tissues which lie in close proximity to the heart, will decrease the amplitude of the electrocardiographic deflections. The question arises, then, as to whether edema of the lungs, pericardial effusion, hydrothroax, ascites, or massive edema of all the body tissues may not decrease the amplitude of the electrocardiographic deflections." In 1 of the cases of rheumatic heart disease coming to necropsy, previously mentioned in this paper, the maximum voltage was 4.5 mm. This case showed dense, pericardial adhesions extending out into the mediastinum. One of the patients with hemopericardium and 1 with pyopericardium reported by Scott, Feil and Katz[17] showed monophasic curves of normal voltage.

It is suggested that the low voltage curves seen in our series of 11 cases of chronic increased pericardial pressure (all of whom were without evidence of vascular disease) were due to the dense adhesions surrounding the heart. Low voltage also occurs with myocardial fibrosis secondary to the narrowing of the lumen of the coronary vessels, and occurs with myxedema.[18] The characteristic clinical pictures are of aid in the differentiation of these latter conditions.

Summary. Eleven patients with adhesive mediastinopericarditis, upon whom pericardectomy was performed, all had electrocardiograms with *Q–R–S* complexes of low amplitude. The *T* waves were low in voltage. Following pericardectomy the *Q–R–S* voltage increased in 4 of 7 cases.

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COMPLETE AURICULO-VENTRICULAR DISSOCIATION.

A CLINICAL STUDY OF SEVENTY-TWO CASES WITH A NOTE ON A CURIOUS FORM OF AURICULAR ARRHYTHMIA FREQUENTLY OBSERVED.

BY ASHTON GRAYBIEL, M.D.,

AND

PAUL D. WHITE, M.D.,

BOSTON, MASS.

(From the Cardiac Clinic, Massachusetts General Hospital.)

THIS report deals with certain clinical features of a group of 72 patients who, on at least one occasion, revealed complete auriculo-ventricular dissociation; it is designed to supplement and extend the observations published in 1923 by White and Viko.[1] Recently

Ellis[2] reported 43 cases of complete heart block analyzed from a point of view somewhat like that we have employed in this paper.

Although complete *A–V* block may be suspected from clinical observations, objective registration representing auricular and ventricular contractions is necessary for final proof. This proof was obtained electrocardiographically in each of our 72 cases. The rare instances of complete *A–V* dissociation, occasioned by the automatic capacity of some lower center exceeding that of the normal pacemaker, have not been included.

Consideration of the Group as a Whole. Of the 72 patients there were exactly twice as many males as females (Table 1). The age incidence was overwhelmingly greatest in the later decades of life although instances occurred in the entire range from infancy to very old age.

TABLE 1.—NUMERICAL AND SEX DISTRIBUTION OF CASES ACCORDING TO THE PROBABLE ETIOLOGY OF THE A–V BLOCK TOGETHER WITH THE AVERAGE AGE OF EACH GROUP.

	Male and female.		Male.		Female.	
Probably etiology of *A–V* block.	No.	Average age.	No.	Average age.	No.	Average age.
Coronary heart disease	47	63.0	36	62.6	11	63.4
Congenital heart disease	4	5.7	1	0.3	3	7.5
?Congenital heart disease	2	22.5	..	....	2	22.5
Rheumatic heart disease	3	41.6	2	45.5	1	34.0
Luetic heart disease	3	42.6	3	42.6	..	....
?Diphtheritic heart disease	4	34.7	1	28.0	3	37.0
Rheumatic, luetic or coronary heart disease	1	48.0	1	48.0	..	....
Coronary or luetic heart disease	2	46.0	2	46.0	..	....
Coronary or rheumatic heart disease	4	50.7	2	55.5	2	46.0
Entirely uncertain	2	34.5	..	....	2	34.5
Total	72	52.6	48	56.7	24	44.5

The probable etiological factors were congenital defects in 6, diphtheria in 4, rhematic fever in 3, syphilis in 3, and arteriosclerotic coronary disease in 47; in the remaining 9 either the causal factor was unknown or multiple factors were present.

At the time complete *A–V* block was first proven in 66 of our 72 cases, the average duration of cardiac symptoms was 2 years and 9 months. The functional cardiac status was as follows: 7 had normal cardiac reserve, 11 a slight decrease, 31 a moderate decrease, 11 a marked decrease, and 6 had frank congestive failure. Attacks of dizziness, syncope or convulsions, symptoms related to the block itself, were present in about $\frac{2}{3}$ of the patients; measures directed toward the relief of these symptoms were largely unsuccessful. Digitalis was given to 20 patients; it was of significant value in relieving heart failure in 4, notwithstanding the slow ventricular rates.

The ventricular rates, obtained from the initial electrocardiograms showing complete *A–V* block, ranged from 19 to 71 a minute and averaged 40; in 17 instances there was more than 5% variation in the time between the slowest and fastest rates. Partial or complete bundle branch block was present in 48 of the 72 electrocardiograms, auricular fibrillation in only 2, auricular standstill in 1, and premature ventricular beats in 10.

We were able to obtain subsequent information, at least in regard to life or death, in 68 of the 72 cases. The average duration of life after the initial record showing complete *A–V* block, in 41 patients dying of cardiovascular disease, was 2 years and 2 months; in 8 dying of some affection other than heart disease, 6 years and 8 months; in 17 remaining alive, 6 years and 11 months.

There is little to be gained in studying these cases as a single group since the heart disease responsible for the block usually affects the clinical course, treatment, and prognosis more than does the block itself. Because of this they have been grouped with regard to etiological considerations.

Coronary Heart Disease and Complete A–V Block. This group comprises 47 cases in which coronary heart disease was quite certainly the cause of the heart block; arterial hypertension was an associated finding in 25 of the 47.

The males outnumbered the females more than 3:1; there were 36 of the former and 11 of the latter.

The average age at which complete *A–V* block was first proven was the same for both sexes, 62 years. The extremes in age were 47 and 85 years. There were 5 patients in the fifth decade of life, 12 in the sixth, 19 in the seventh, 9 in the eighth, and 2 in the ninth.

The average duration of symptoms before the discovery of complete *A–V* block was 2 years and 8 months and was nearly twice as long in the females as in the males. At the time complete *A–V* block was first proven an evaluation of the degree of heart failure was made in 43 of the 47 cases. In only 1 of these was the cardiac reserve considered normal, in 5 it was slightly decreased, in 20 moderately decreased, in 11 markedly decreased, and in 6 there was frank congestive failure.

Coronary thrombosis was responsible for the onset, simultaneously, of cardiac symptoms and complete *A–V* block in 6 patients, in 3 of whom it was fatal; 1 additional patient suffered a fatal attack of coronary thrombosis after the discovery of the conduction defect. Angina pectoris was present in 9 patients at the time block was first discovered and developed after the onset of block in one other.

In addition to the usual symptoms of cardiac weakness 32 of the 43 patients, concerning whom the data were complete, suffered attacks caused presumably by cerebral anemia; 11 had dizzy spells, 20 had syncopal attacks, and 1 had syncope with convulsions. Three patients experienced only one attack of dizziness or syncope

while the remaining 29 suffered many attacks. Such attacks heralded the onset of cardiac symptoms in 8 patients, while in 4 they were the probable cause of death.

Arterial blood pressure, in 40 of the 47 cases, averaged 173 mm. Hg systolic and 83 mm. Hg diastolic. In 24 of the 25 with coronary and hypertensive heart disease the average pressure was 203 mm. Hg systolic and 88 mm. Hg diastolic, while in 16 patients with coronary disease without hypertension the average pressures were 128 mm. Hg systolic and 74 mm. Hg diastolic. There was no substantial difference in pressures between the sexes. Only occasionally were low diastolic pressures recorded. The lowest was 50 mm. Hg and the accompanying systolic pressure was 140; aortic regurgitation was not present in that case.

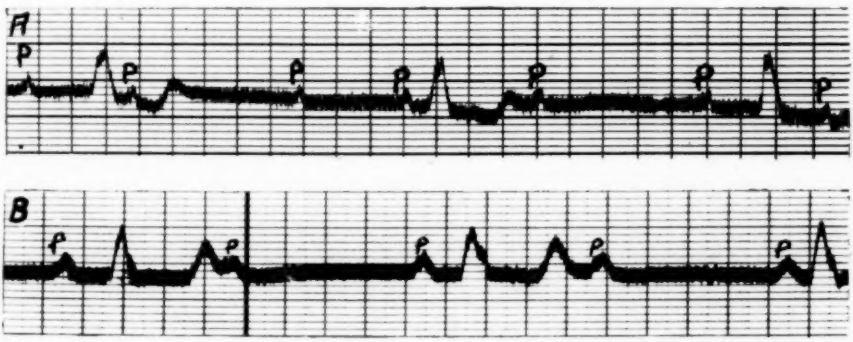

FIG. 1.—*A* shows a lengthening of the second auricular cycle while the third cycle is similar in duration to the first. The fourth auricular cycle is longer than the first or third, and may be due to the early occurrence of the ventricular contraction in this cycle. *B* shows a less marked example of auricular arrhythmia.

The initial electrocardiograms showing complete *A–V* block were analyzed. The average ventricular rate was 38 a minute; the extremes were 20 and 64; in 8 instances there was more than 5% variation in the time between the slowest and fastest ventricular rates. The average auricular rate was 86. There was little or no correlation between auricular and ventricular rates. In 35 of the 47 electrocardiograms there was partial or complete bundle-branch block; auricular fibrillation occurred in 2 instances, auricular standstill in 1, and ectopic ventricular beats in 10.

Subsequent electrocardiograms were taken in 25 cases; in 16 the *A–V* block remained complete, in 5 there was a return to partial *A–V* block, and in 4 the *A–V* conduction time returned to normal.

The treatment of patients in this group was directed chiefly toward the failing heart muscle and followed the usual plan. Digitalis was given and its effect noted in 16 patients; in 3 it was appreciably beneficial while in 13 it was not.

Treatment designed to increase the heart rate or to abolish the

cardiocerebral (Adams-Stokes) attacks was attempted with 30 patients. Adrenalin was given to 2 patients with good effect, its use being limited by the inconvenience of administration and short-lived action. Ephedrin, given to 7 was beneficial in 3, without benefit in 3, and in 1 it caused troublesome palpitation. Thyroid extract was given to 7 patients with questionable benefit to 1. Barium chlorid ($\frac{1}{2}$ to 1 gr. t.i.d.) was used in 8 cases without benefit to any. Atropin was given to 6 patients without benefiting any. In 1 patient a slight fever caused the pulse rate to increase from 40 to 60 where it remained for a period of 5 days after the temperature returned to normal. In a few patients the avoidance of certain things which sometimes precipitated attacks constituted the best treatment.

The average duration of life, in 45 of the 47 cases, after complete *A–V* block was recognized, was as follows: 1 year and 7 months in the 30 cases dying of cardiovascular disease; 6 years in the 6 cases dying of various other causes; and 3 years and 10 months to date in the 9 cases remaining alive. The longest duration of life was 16 years and 5 months; in 12 instances the duration of life was over 4 years, while in 18 it was less than 1 year.

The causes of death in the 30 cases dying of cardiovascular disease were listed as follows: congestive heart failure in 4, Adams-Stokes attacks in 4, coronary thrombosis in 4, cerebral accident in 2, "sudden death" in 7, and "heart disease" in 9.

Congenital Heart Disease and Complete A–V Block. There were 4 cases, 1 male and 3 female, in which the heart block was assuredly of congenital origin. The average age was 5 years and 8 months. None had had diphtheria, rheumatic fever, congenital lues, or scarlet fever. The heart was slightly enlarged in 2 cases. Patency of the interventricular septum was questioned in 3, but the classical signs of such a defect were not present. It is important to note that there was no other definite evidence of congenital heart disease save the complete *A–V* block. If these cases had been first seen in later life the etiology would be uncertain or possibly wrongly ascribed to some other factor. Cardiac reserve was normal in 3 cases and slightly decreased in 1. None had had dizzy spells or syncopal attacks.

The electrocardiograms showed an average ventricular rate of 59, the extremes being 49 and 71; the average auricular rate was 130. In 2 instances there was marked variation between the slowest and fastest ventricular rates. In addition to complete *A–V* block the electrocardiogram in 1 instance (an infant of 9 months) showed inversion of *T* in Lead I, and in one other, partial bundle-branch block.

We have been unable to trace 2 patients, lack of cardiac symptoms probably being responsible for their losing touch with the

clinic. The cardiac status of the remaining 2 has not changed over periods of 1 year, and 7 years and 9 months respectively.

Two additional patients probably belong to this group. Both were female, 1 aged 12 years and the other 31. Neither had had diphtheria, rheumatic fever, syphilis, or scarlet fever. Both had been free from dizzy spells and syncopal attacks. The older patient had slight cardiac enlargement and slight dyspnea, while the younger had no cardiac symptoms and a normal sized heart. The cardiac status remains unchanged after 4 years and 4 months in the case of the older patient, and 18 years and 6 months in the case of the younger.

Rheumatic Heart Disease and Complete A–V Block. There were 2 men and 1 woman in whom the probable cause of complete *A–V* block was rheumatic heart disease. One of the men, aged 48, had a normal sized heart. He had no symptoms whatever and the electrocardiogram, in addition to complete *A–V* block, showed at times block of the ventricular pacemaker.[3] Later his heart enlarged and attacks of dizziness, and symptoms of heart failure appeared in moderate degree. He died following an operation 17 years after the onset of block which always remained complete. Necropsy revealed mitral stenosis; the coronary arteries were freely patent. No detailed postmortem studies of the conductive system were made.

The other man, aged 43, had a markedly enlarged heart with aortic and mitral stenosis without congestive failure. For 1 week he had had many severe attacks of dizziness, syncope, and convulsions. He contracted bronchopneumonia and died 3 days after the discovery of block. Necropsy was not performed.

The 1 woman in this group, aged 34, had a slightly enlarged heart with mitral stenosis and aortic regurgitation. She had had cardiac symptoms for 11 years and syncopal attacks for 1 month. An electrocardiogram showed low voltage in addition to complete *A–V* block. She was observed over a period of 2 years and 6 months during which time her cardiac status remained about the same and the block remained complete. Further efforts to trace this patient have failed.

Luetic Heart Disease and Complete A–V Block. Three male patients with an average age of 43 years comprise this group. They all complained of cardiac symptoms and the cardiac reserve was moderately decreased in each. One had angina pectoris and 1 other had syncopal attacks. All had moderately enlarged hearts, and one had aortic regurgitation. Their blood pressures averaged 133 mm. Hg systolic and 55 mm. Hg diastolic. The Wassermann reaction was positive in 2 and the third showed luetic cardiovascular changes at necropsy. No detailed postmortem studies of the conductive system were made. In addition to complete *A–V* block the initial electrocardiograms showed in each case partial or complete

bundle branch block also, in 1, retrograde auricular responses, and in 1 other, a block of the ventricular pacemaker. One patient who received inadequate antiluetic treatment died of heart failure in 8 months. The remaining 2 cases received prolonged antiluetic therapy. The block remained complete in 1 but there was a return to normal rhythm in the other with partial bundle branch block remaining. Both were quite well and worked hard for years. One died suddenly 7 years and 10 months after the discovery of the block and necropsy revealed luetic aortitis with marked narrowing of the first portions of the coronary arteries. The other died of "heart disease" 4 years after the discovery of the block.

Diphtheritic Heart Disease and Complete A–V Block. Chronic heart block can rarely be traced to diphtheria. Jones and White,[4] in a study of 100 consecutive cases who had had severe diphtheria 5 to 8 years previously, found none with evidence of heart disease. Butler and Levine[5] have reported 20 cases of heart block of unknown origin, 10 of which previously had had diphtheria; of the 10 cases with a history of diphtheria only 3 were under 50 years. It appeared to them that the development of heart block in later years may be a sequel to diphtheria in childhood.

In the following 4 cases of complete *A–V* block the only known etiologic factor was previous diphtheritic infection. Each had proven complete *A–V* block or syncopal attacks at an age when coronary heart disease was unlikely. None had any evidence of congenital heart disease although this possibility could not be ruled out definitely. Three had had diphtheria early in life and were aged 24, 27, and 28 years, respectively, when first examined by us; each had slight cardiac enlargement but none had attacks of dizziness or syncope and their response to exercise was normal. The fourth, aged 60, had had diphtheria 25 years previously and from that time suffered frequent attacks of dizziness and syncope; the heart was not enlarged but exercise tolerance was moderately decreased.

Repeated electrocardiograms in each instance showed complete *A–V* block.

Three of the patients are alive and fairly well at an average of 14 years and 8 months after the discovery of the conduction defect. The fourth case, aged 60, died of "heart disease" 4 years after the proof of the block and 29 years after the probable onset.

The response to exercise and atropin in 1 patient of this group is of some interest. While at rest the auricular rate was 60 and the ventricular 43. After exercise the auricular rate rose to 143 and the ventricular rate to 107, the block remaining complete. A similar but less marked rise was observed after gr. $\frac{1}{30}$ atropin sulphate was given subcutaneously. The explanation was not entirely clear; presumably the factor responsible for the block had not destroyed the vagal influence on the idioventricular pacemaker.

Miscellaneous. There remain for consideration 4 cases with coronary and rheumatic heart disease, 2 with coronary and probable luetic heart disease, 1 with coronary and probable luetic or rheumatic heart disease, and 2 with completely uncertain etiology. For obvious reasons it is not worth while to consider these cases in detail.

There were 5 males and 4 females with an average age of 45 years. All had some degree of cardiac enlargement and all had symptoms of cardiac weakness. All save 2 had cardiocerebral attacks. Seven have died of cardiovascular disease on an average of 2 years and 4 months after discovery of the block, while 1 remains alive but in poor health 6 years and 8 months after the discovery of the block. The remaining case was alive and well when last heard from in May, 1927.

Discussion. Only 72 patients with complete *A–V* dissociation have been seen at this hospital during a period of 19 years in which time electrocardiograms have been taken on about 14,000 patients.

While coronary heart disease was found to be the chief cause of the block it is worth noting that in about one-fourth of the cases other factors were responsible, namely, congenital, rheumatic, luetic, or diphtheritic heart disease. Some additional causes, not illustrated in this series of cases, are certain acute infections, poisoning, especially by drugs of the digitalis series, tumor, and trauma.

The sex and age incidence reflect that of the disease causing the block. Thus, patients with coronary heart disease were in the later decades of life and males outnumbered females more than 2 to 1, whereas patients with congenital heart disease were in the early decades of life and females outnumbered the males.

The cardiac symptomatology may be divided into two categories, that associated with the underlying heart disease and that associated with the block itself. The latter deserves especial mention.

Morgagni,[6] in 1761, adequately described the syndrome of fainting associated with slow pulse rate but his report went unrecognized for many years. Adams,[7] in 1827, and Stokes,[8] in 1846, described more fully additional cases, and Huchard,[9] in 1899, proposed the name of "disease of Adams or of Stokes-Adams" for this syndrome of bradycardia and syncope. Lewis[10] has pointed out that "however probable it is that heart disease and high-grade block were present in these cases, the exact nature of the fits is unknown." Regardless of its unsuitability, it appears that the term Adams-Stokes or Morgagni-Adams-Stokes attacks will persist, although a decidedly better classification could be outlined under the heading of cardiocerebral attacks. Three grades of disability are commonly recognized: 1, the vertiginous attacks ("formes frustes" of Huchard) in which consciousness is not lost: 2, syncopal attacks and 3, convulsive seizures. These symptoms are caused by cerebral anemia and occur when the ventricles beat too slowly or stop entirely.

About two-thirds of the patients in our own series complained of attacks of dizziness, syncope, or convulsions.

The average ventricular rate in this series of cases was 40 a minute, which is faster than is commonly thought for complete *A–V* block. In 17 instances (23.6%) there was a greater than 5% variation in the time between the slowest and fastest ventricular rates. This arrhythmia when coupled with the more rapid ventricular rates adds difficulty to the clinical recognition of complete *A–V* block.

Partial or complete bundle-branch block was an associated finding in 42 instances (58.3%). This association is expected in view of the small area occupied by the bundle of His and its chief branches.

The slow regular heart rate observed in these cases rarely requires treatment; in fact it may occasionally be an asset. It is when the ventricles beat very slowly or become irregular that symptoms supervene and efforts are made to increase the rate or abolish the irregularity. Adrenalin and ephedrin were the only drugs found valuable in our series.

The prognosis of the patients in this series reflected that of the causal factor responsible for the block. For those with coronary heart disease it was poor, although exceptionally a patient lived more than 10 years.* The prognosis was very good in those with congenital or diphtheritic heart disease while in those with luetic or rheumatic disease it was fair. The outstanding impression gained after reviewing these cases is the necessity for distinguishing clearly between the conduction defect and the heart disease with which it may be associated. When complete *A–V* block is present in an otherwise normal heart the bearer may enjoy a normal active life. Its chief significance does not lie in itself for it is rarely the immediate cause of death, but in the fact that it usually declares the presence of a serious and widespread affection of the ventricular musculature; as such it is an important sign and alters unfavorably the prognosis.

A Curious Form of Auricular Arrhythmia Frequently Observed in Complete Heart Block. Erlanger and Blackman[11] in their studies on experimental complete heart block in the dog, observed, occasionally, a peculiar periodicity of the auricles apparently dependent upon ventricular activity. They noted that the first auricular cycle following a ventricular contraction was long but that the successive auricular cycles shortened until the ventricle again contracted. Sometimes this auricular retardation was so marked that only a single contraction occurred in each ventricular cycle. This phe-

* Two exceptional instances of heart block in very elderly patients are worth mentioning. H. L., a widow, with coronary heart disease, had complete heart block for 4 years before she died of intestinal obstruction at the age of 86. F. M., a male clerk, aged 80, has had partial or complete heart block over 12 years; at present he is slightly active and fairly well.

nomenon was observed only during complete repose in dogs with heart block of comparatively long duration. They believed variations in vagal tonus, which increased with each arterial pulse and decreased during the interval between pulses, were responsible.

Hecht,[12] in 1913, published electrocardiograms showing high grade block found in a child of 5 years. He noted that the auricular cycles which contained a ventricular contraction were shorter than the rest. No explanation was offered and he did not comment on the electrocardiogram which showed that the arrhythmia was abolished when the child was given atropin. Wilson and Robinson[13] observed the same kind of auricular arrhythmia in a case of complete heart block in an adult. They observed the disappearance of this arrhythmia when the auricular rate was increased after exercise or atropin. Two possible explanations were offered; first, that it was dependent on vagus activity, and second, that it was the mechanical effect of ventricular systole on the auricular pacemaker.

We have observed this type of auricular arrhythmia (Fig. 1) in 20 of the 72 cases in this series. It was not necessarily a constant phenomenon; that is, it would be exhibited on one occasion but not on another under circumstances apparently similar. It was observed to disappear with the increase in auricular rate after atropin or other cause. When the ventricular period contained two or more auricular cycles it was seen that the first auricular cycle following the ventricular contraction was long and the successive cycles shorter.

In considering the possible mechanisms of this arrhythmia one of the first points to decide is whether the auricular cycle containing the ventricular contraction is shortened or whether the succeeding auricular cycle is lengthened. This question is apparently answered in those examples where the ventricular period contains two or more auricular cycles. It is clearly to be seen that it is the first auricular cycle following the ventricular contraction which differs notably from the rest; the remaining cycles are shorter and do not differ greatly in length whether or not they contain a ventricular contraction. This leaves little to be said in favor of the view that the auricular cycle containing the ventricular contraction is shortened by the mechanical effect of ventricular systole on the auricular pacemaker; were this true all subsequent auricular cycles should be similar in length. We are inclined to the opinion that under certain conditions ventricular systole increases vagal tone possibly through the carotid sinus mechanism or directly through the arterial impulse in the sino-auricular artery or otherwise. We believe this is the usual mechanism, although very exceptionally electrocardiograms have been observed, apart from those instances of obvious ventriculo-auricular retrograde conduction, in which certain ventriculo-auricular sequences suggested that ventricular systole hastened auricular contraction. We have not observed this form

of ventriculo-auricular relationship in any of the electrocardiograms in this series.

Summary and Conclusions. 1. Seventy-two cases of complete *A–V* dissociation are briefly analyzed. Coronary heart disease was associated in 47 of the patients, congenital heart disease in 4, possible congenital heart disease in 2, rheumatic heart disease in 3, cardiovascular lues in 3, and possible chronic diphtheritic heart disease in 4, while the remaining 9 cases were of mixed or entirely uncertain etiology. Two-thirds of the cases (48) were male and one-third (24) were female; it was particularly in the coronary disease and syphilitic groups that the males predominated (36 to 11 in the former and 3 to 0 in the latter).

2. The heart disease responsible for the block in these cases affects the clinical course, treatment and prognosis far more than does the block itself.

3. Attacks of dizziness, syncope, or convulsions, symptoms related to the block itself, were present in 44 of the 72 cases; in 4 instances they were the probable cause of death. Adrenalin and ephedrin were the only drugs found valuable in the treatment of these attacks.

4. The prognosis of those patients in this series with coronary heart disease was generally very poor although there were striking exceptions; for those with congenital or old diphtheritic heart disease it was good, while for those with luetic or rheumatic disease it was fair.

5. A form of auricular arrhythmia frequently observed in these cases is discussed.

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OBSERVATIONS ON SOME OF THE PHYSIOLOGIC EFFECTS OF THE CORRECTION OF FAULTY POSTURE.

By Louis B. Laplace, M.D.,
ASSOCIATE IN CARDIOLOGY, GRADUATE SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA,
AND
Jesse T. Nicholson, M.D.,
ASSOCIATE IN ORTHOPEDIC SURGERY, GRADUATE SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA, PA.

(From the Departments of Cardiology and Orthopedic Surgery.)

The correction of faulty posture involving the thoracic and lumbar spinal curves has been considered a mechanical advantage to the body and a valuable adjunct to the treatment of many visceral disorders.[1] This belief is supported by considerable clinical evidence. Faulty posture is certainly capable of producing various symptom complexes of referred pain which may be completely relieved by training the patient to assume a proper stance. If, however, the routine correction of postural defects is to be granted a position in the generally accepted treatment of disorders which are not essentially orthopedic, more precise information should be available concerning the influence of posture on the body function. An attempt has, therefore, been made to estimate some of the physiologic effects of changing from a kypho-lordotic posture to one regarded as optimum by orthopedic standards. The present study involves an analysis of the immediate results so observed. It is believed that these observations help to evaluate the therapeutic benefit to be expected from the orthopedic correction of postural defects.

Methods. A group of subjects was studied, which included 18 healthy adults of both sexes with B, C, and D posture according to the Harvard standards. Ten subjects were workers in the Occupational Therapy Clinic of the Graduate Hospital and symptom-free; 8 were patients of the Orthopedic Clinic who had symptoms referable to faulty mechanics. All had been trained in the ability to correct their postural defects.

All observations reported on each patient were obtained on the same day to insure comparable results, although preliminary periods of observation were usually made. The following studies were carried out with the subject standing first in the corrected, then in the faulty posture. 1. Orthodiagrams with special attention to the thoracic and cardiac measurements and the maximum diaphragmatic excursion. (Difference of less than 0.5 cm. were regarded as within the limit of experimental error. Diaphragmatic measurements were made from the highest point of the dome.) 2. Estimations of vital capacity obtained with a standard spirometer (the figures reported are the averages of the maximum values). 3. Electrocardiograms. 4. Estimations of oxygen consumption and graphic records of the respiration including measurements of tidal air and minute volume, obtained with a standard spirometer for metabolism determinations. 5. Repeated determinations of blood pressure and pulse rate over 10-minute intervals with preceding and intervening 10-minute intervals during which the subject was recumbent. On the basis of these readings a rating was obtained for circulatory efficiency in each of the two postures according to the method of Turner.[2]

Results. The changes observed on correcting a faulty posture are outlined in Table 1. It will be noted that there was a marked individual variation in the reaction of the different subjects and that the results bear no apparent relationship to their postural classification, whether B, C or D. These variations appeared to depend upon such factors as physical type, the extent of the physiologic handicap produced by the postural defect and the amount of physical strain incurred by correcting it. Thus the first conclusion which can be drawn is the fact that the therapeutic value of correcting a postural defect can seldom be estimated beforehand and that the amount of benefit acquired is not always directly proportional to the degree of the subject's "slump."

Transverse Diameter of the Chest. The measurements of the transverse diameter of the chest were made in the position of normal expiratory relaxation. Of the 18 subjects, 9 showed no significant change on correcting the faulty posture, 7 showed a slight increase of 0.5 to 1.8 cm., while 2 showed a decrease of approximately the same value. Apparently the chest becomes somewhat wider in the presence of either extreme correction or extreme slump. In the correct posture, straightening of the spine causes an increase in the rib angles with outward flaring of the chest. In the excessively slumped posture, the lower part of the chest tends to widen due to upward compression of the abdominal viscera.

Position of the Diaphragm. Orthodiagraphic illustrations of the chest in the corrected and slumped postures always show the diaphragm higher in the former.[1] In our experience this relationship has not been constant. In 7 cases the diaphragm was higher in the corrected than in the faulty posture (*i. e.*, with respect to the top of the chest); in 4 there was no significant difference between the two positions; in 7 the diaphragm was higher in the slumped posture (Fig. 1). This difference may be explained as follows: On assuming a corrected posture, the abdominal wall is drawn in and the diaphragm pushed upward. At the same time the thoracic spine straightens and the chest elongates on its vertical axis. The diaphragm, therefore, is raised with relation to the pelvis but not necessarily with relation to the top of the chest. This fact is of considerable interest. If coincident elongation of the chest does not occur, the elevation of the diaphragm will diminish the chest volume and may become a handicap to pulmonary function. Thus in the presence of irretractable kyphosis it may be a disadvantage to cause elevation of the diaphragm if an adequate increase in thoracic volume cannot be obtained by straightening of the thoracic as well as the lumbar spine. This is not necessarily a handicap in cases of emphysema where the lung is already overexpanded as it has been shown that elevation of the diaphragm permits increase in the vital capacity.[3]

Position of the Heart. Change from a faulty to a corrected posture is said to involve an increase in the transverse diameter of the

TABLE 1.—THE EFFECTS OF CORRECTION OF POSTURAL DEFECT.

Subject	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	Average		
Posture class	C	B	C	C	C	D	C	C	C	C	D	D	C	C	C	B	D	D	+	−	0
Transverse diameter of chest	0	0	0	−	+	0	0	+	0	+	0	+	0	−	+	+	+	0	7	2	9
Height of diaphragm	−	−		+	0.5	−		0.6	+	1.7	+	1.8	−	0.5	−	0.5	−	+			
	1.5	0.7	0	0.6	0	1.5	0	0	1.6	0.8	1.9	0.7	1.0	2.5	1.7	2.1	0.8	1.2	7	7	4
Transverse diameter of heart	−	−	−		−	−				+		+	−	+	+		−				
	0.6	1.5	1.1	0	0.7	0.5	0	0	0	1.3	0	0.7	1.7	0.5	1.0	0	0.6	0	3	8	7
E. C. G. axis shift toward left	−	−	0	0	+	−	0	+			+	+	−	+	−	−	0		5	7	4
Excursion of diaphragm	+1.5	+1.8	+1.0	−1.2	−3.4	−0.5	−1.5	0	+1.6	−1.8	+1.5	+0.8	−1.0	+2.0	+1.0	+1.6	−1.4	−0.9	7	7	4
		−0.7					+0.9		−0.7												
Vital capacity . .	0	0	+100	+510	0	+110	+404	+116	0	+494	+260	+575	+257	0	0	+240	−360	0	10	1	7
Respiratory rate . .	+3	−4	−8	+2	0	0	−10	−2		−5	0	−1	−11	+3	−3	+3	−1	−2	4	10	3
Tidal air	−55	+825	+545	+232	+48	0	+333	+106		+625	+341	+171	+668	−254	+166	+122	+510	+26	14	2	1
Respiratory minute volume	+	+	+	+	+	−	−	+		+	+	+	+	−	+	+	+	0			
	320	5480	3030	4120	1010	480	470	1190		4270	1520	6030	980	2500	4880	8720			13	3	1
Oxygen consumption	0	−103	+17	0	−30	+67	+40	−76		0		−46	+36	+36	0	−57	+233	0	6	5	5
Circulatory efficiency	0	+14	0	+8	+2	+4	−1	+4	−6	+9	+?	0	+2	−3	−3	+15	+1	+3	11	4	3

0 = no change upon shifting from a faulty to a correct posture; + = increase; − = decrease.

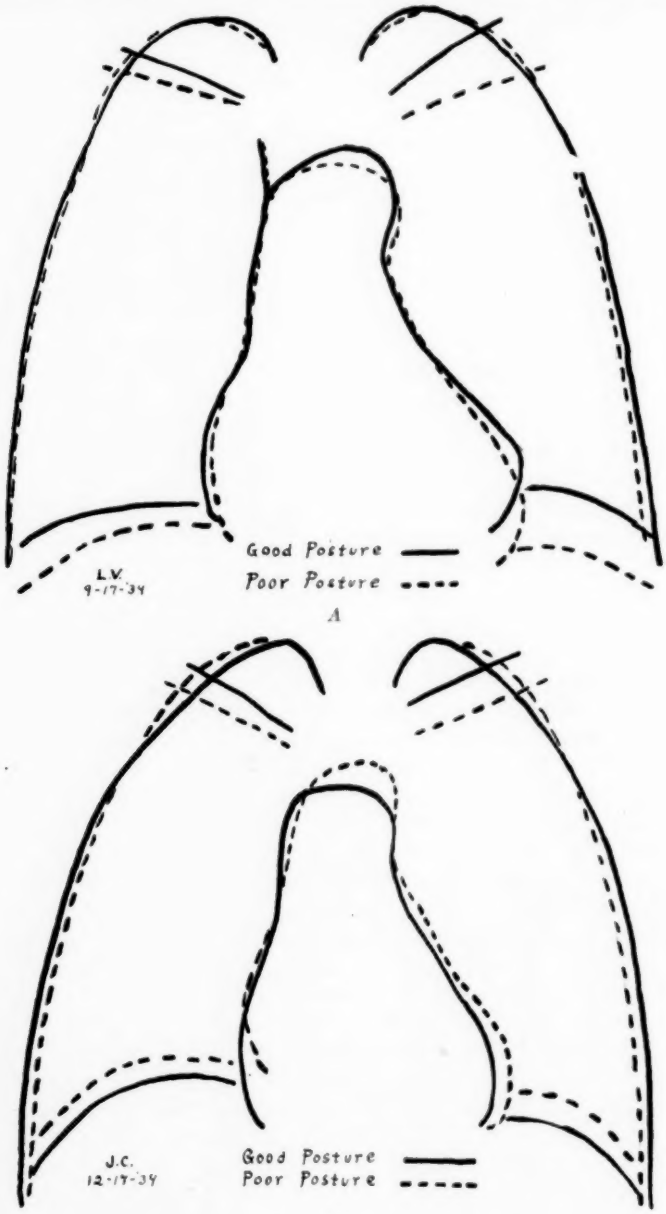


FIG. 1.—Orthodiagram: broken line indicates poor posture; continuous line, good posture. *A*, shows Subject 14 in whom the diaphragm is higher with respect to the top of the chest and the heart more transverse in the corrected posture. *B*, shows Subject 15 in whom the diaphragm is lower with respect to the top of the chest and the heart is less transverse in the corrected posture.

heart due to elevation of the diaphragm.[1] In the present study it was found that just as the height of the diaphragm with respect to the top of the chest is not always increased by the correction of a postural defect, neither does the heart always become more transversely placed. In only 3 cases was the cardiac transverse diameter significantly increased; in 7 it remained unchanged while in 8 it was actually diminished. This observation was confirmed by the electrocardiogram, which in the corrected posture showed the electrical axis of the heart to be shifted toward the left in 5 cases and toward the right in 7, while in 4 it remained unchanged. In 10 cases the axis shift corresponded with the observed change in the cardiac measurement; in only 1 case was it at variance. In the remaining cases either the electrical axis of the heart or the measured transverse diameter was unchanged.

Although the transverse diameter of the cardiac silhouette tends to increase when the diaphragm is elevated by the corrected position, it may actually decrease under the following circumstances: 1, when the heart is sufficiently elevated by its attachments to the cervical fascia and, therefore, becomes more dependent; 2, when the heart is elevated by the rise of the diaphragm rather than by upward traction of its mediastinal attachments, but tends to rotate in a horizontal rather than a vertical direction. The degree to which these phenomena occur varies between individuals and with the physical type of chest and its contents and could be observed under the fluoroscope. The occasional lack of correspondence between the measured cardiac silhouette and the angle of the electrocardiographic axis depended upon the fact that the two are similarly altered by vertical rotation of the heart but not necessarily by horizontal rotation or lateral displacement.

Diaphragmatic Excursion. The maximum diaphragmatic excursion between forced inspiration and expiration occurred in the corrected posture in 7 cases and in the slumped posture in 7. In 4 cases the change was not considered significant. This difference in some subjects was apparently due to the upward compression of the diaphragm in the correct posture being predominantly advantageous by favoring a more complete expiration; in others it was predominantly a disadvantage by impeding inspiration. As will be shown later, the extent of the maximum diaphragmatic excursion is not directly proportional to either the vital capacity or the average depth of respiration, both of which are influenced by thoracic excursion as well. It is clear from these observations that the posture which is most favorable to diaphragmatic function may, for certain individuals, be one which is not perfect by orthopedic standards.

Vital Capacity. In 10 cases the vital capacity was increased on assuming the corrected posture (average when increased, 307 cc.), in 7 cases it was not significantly altered and in only 1 case was it decreased. Although there is no doubt as to the improvement of the

vital capacity in the corrected posture, it was noted that when erect many of the subjects stooped somewhat to complete expiration, and when slumped they became momentarily more erect during the preliminary inspiration. From this it appears that although an increased vital capacity is favored by the corrected posture, too rigid correction may tend to diminish it and a certain flexibility is requisite for optimum results.

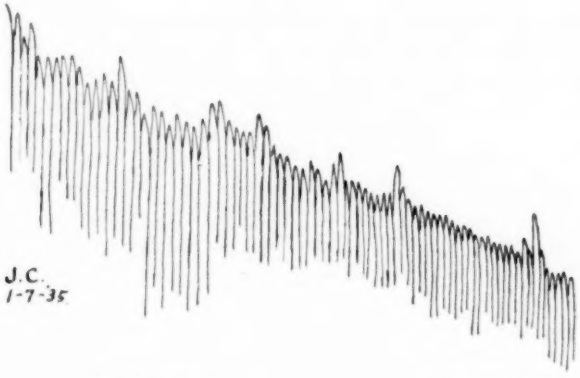
The vital capacity is intimately related to cardiac and respiratory function. It is decreased in the presence of various disorders of the heart and lungs. In cases of this type an optimum stance is often assumed instinctively. In such cases it is probably a mistake further to correct a minor postural error, since to do this may produce a physiologic handicap. Other patients, however, because of fatigue or the therapeutic restriction of exercise, become increasingly relaxed and stooped. Under these circumstances it is justifiable to expect that an increase in the vital capacity attained by orthopedic training may afford a marked degree of symptomatic benefit. Care should be taken, however, that the posture so assumed is actually optimum for the individual and that the circulation is not further embarrassed by too rapid correction.

Electrocardiogram. No significant changes in the electrocardiogram were found which were attributable to posture, except for a shift in the electrical axis of the heart described above. This shift was indicated by variations in amplitude of the *R* and *S* waves in Leads I and III. Rarely the amplitude of the *T* waves in Lead III was similarly influenced but to a very slight degree.

Incidentally records taken in the corrected posture of many subjects showed a much higher degree of muscle tremor than those taken in the slumped posture. This was a manifestation of greater physical strain associated with the unaccustomed posture and indicates the fatiguing effect of maintaining it for long periods of time.

Oxygen Consumption. The measurements of oxygen consumption are necessarily subject to a considerable degree of experimental error and can be considered significant only in the direction and not in the quantity of change. Of 16 subjects in whom estimates could be made, 5 showed no difference in the two positions, 6 showed the highest value in the good posture and 5 in the poor posture. The rate of oxygen consumption under the circumstances is influenced by many factors including the fatigue of standing, the relative degree of strain involved by the corrected posture, the amount of respiratory effort and the amount of oxygen available to the tissues. Although these results are at best only suggestive, the impression was gained that oxygen normally tends to be utilized somewhat less rapidly in the corrected posture. In the present study the effect of strain in subjects whose habitual stance was slumped was very apparent, especially in the electrocardiogram. If this strain were eliminated by adaptation to the corrected posture, it is likely that the higher oxygen consumption values would be definitely reduced.

Respiration. The effects on respiration of the corrected as compared with the slumped posture included: 1, Slower rate; 2, increased depth of respiration (tidal air) and 3, increased pulmonary ventilation (respiratory minute volume). The type of graphic record obtained is illustrated in Figure 2. There were a few exceptions but they were not considered significant. The characteristic effects occurred not only in subjects who were accustomed to the correct posture, but also in subjects to whom it was still a physical strain.



	Good posture:	Poor posture:
Resp. rate	13 /min.	21 /min.
Tidal air	1,012 cc.	467 cc.
Min. vol.	12,850 cc.	9,820 cc.
O_2 consump.	263 cc./min.	246 cc./min.

FIG. 2.—Respiration and oxygen consumption in the correct and incorrect postures—Subject 2.

Three artificial influences must be taken into account in considering the graphic respiratory records obtained: 1, The subject breathed through a spirometer (the effect of which was minimized by a "motor blower"); 2, breathed through his mouth, and 3, breathed pure oxygen. Although the records do not represent entirely normal conditions, they are, however, at least comparable and indicate the direction and proportion of change under physiologic circumstances.

In the corrected posture, respiration is apparently facilitated by an increased latitude for diaphragmatic and thoracic excursion (vital capacity) and tend to be deeper and, therefore, slower. Less clear, however, is the reason for the increased respiratory minute volume. It bore no evident relationship either to oxygen consumption or to circulatory efficiency. To what extent it is an artifact due to the type of graphic recording or how much it was influenced by physical strain is uncertain. It seems probable, however, that it is also present, at least to some degree, under normal physiologic conditions.

Cardiovascular Efficiency. The criteria adopted by Turner for the appraisal of cardiovascular efficiency[2] were applied to the estimations of blood pressure and pulse rate taken over 10-minute intervals in the two postures. Eleven subjects had a better rating in the corrected posture, 4 in the slumped posture and 3 showed no significant change. There appeared a tendency in the slumped posture for the pulse rate to increase, for the blood pressure to fall and for both to manifest less stability than in the corrected posture (Fig. 3). In the majority of subjects these differences were not striking and might be overlooked unless compared by circulatory efficiency standards. In Subjects 2 and 16, however, examples were obtained of an extremely unfavorable effect of faulty posture on the circulation. In both cases the blood pressure fell rapidly from its initial level, the pulse rate became markedly accelerated and the patient

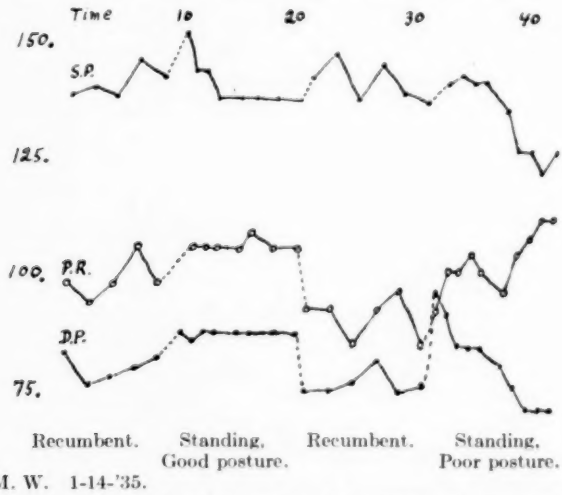


FIG. 3.—Blood pressure and pulse rate in the correct and incorrect postures—Subject 15.

complained of faintness. In the corrected posture these events did not occur. These individuals evidently had a tendency toward postural hypostatic congestion (a condition which is more common than is usually realized). In such cases, hypostatic congestion and the resultant cerebral anemia, may be prevented by the action of the abdominal muscular tone in compressing the splanchnic blood reservoir. This effect, together with the increase in vital capacity, make the correct posture a distinct advantage to cardiovascular function in the majority of cases, while in a few cases its influence may be spectacular.

Discussion. It is again pointed out that these observations concern only the immediate results of change in posture; to what extent the effects are permanent or may be modified by the adaptation of the subject to an improved stance can be determined only after a

lapse of sufficient time and under strictly comparable experimental conditions. There is also an unavoidable element of experimental error associated with the methods employed. But even with due allowance for these factors, we believe that the following opinion is substantiated: Correction of faulty posture is generally a significant advantage to circulatory and respiratory function, and in some cases may have important therapeutic value. All individuals, however, are not equally or similarly benefited. The differences in effect do not appear to depend entirely upon the degree of the defect, but rather upon the degree to which the patient is handicapped by the defect. Full correction of posture is sometimes unfavorable to maximum physiologic efficiency. Too rapid change from a poor to a corrected posture is also likely to be fatiguing and obscure the benefit otherwise derived. Rarely it is possible that an orthopedically faulty posture may be a compensatory adaptation of the body to other abnormalities and should not be changed.

Summary and Conclusions. 1. Eighteen healthy subjects with postural defects of the kypholordotic type were studied with respect to the immediate physiologic changes produced by correction of posture.

2. Corrected posture did not always produce an elevation of the diaphragm with respect to the top of the chest nor did the heart always become more transversely placed. The cause and significance of these facts are discussed.

3. The vital capacity was increased by assuming a corrected posture but it was noted that flexibility of posture was essential in obtaining optimum results.

4. The respirations in the corrected posture became slower and deeper and the respiratory minute volume was increased.

5. The oxygen consumption was not altered in a consistent manner but there was suggestive evidence that under normal conditions it is lower in the corrected than in the faulty posture.

6. Blood pressure and pulse-rate changes on standing indicated in the majority of subjects a better degree of circulatory efficiency in the corrected posture. In 2 cases the corrected posture was able to prevent a postural hypostatic congestion.

7. It was concluded that the correction of postural defects has a significantly beneficial effect on circulatory and respiratory function in the majority of cases. Its value varies considerably between individuals for reasons which are not always evident. In some cases, its effect may be spectacular. Full correction may occasionally be a physiologic handicap. For each individual there is an optimum posture, the attainment of which produces the maximum therapeutic benefit.

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INTRA-ABDOMINAL TORSION OF THE APPENDICES EPIPLOICÆ.

WITH REPORT OF TWO CASES AND REVIEW OF THE LITERATURE.

BY F. A. FISKE, M.D.
CLINICAL ASSISTANT IN SURGERY, TEMPLE UNIVERSITY HOSPITAL, PHILADELPHIA, PA.

(From Senior Surgical Service, Temple University Hospital, Philadelphia.)

THE appendices epiploicæ occur along the entire colon from the cecum to the rectum, being most numerous in the transverse and pelvic colon. They appear in two rows, originating in relation to the anterior muscular band and the postero-internal band; rarely a third row is observed, and occasionally only one row is present. They have been described as pouches or processes of peritoneum, which contain a variable amount of fat, usually considerable in obese persons (Hunt). The blood supply for each consists of one artery and one vein; arising from the superior and inferior mesenteric arteries, and emptying into the superior and inferior mesenteric veins.

The physiologic function of the appendices epiploicæ is not clearly understood. Robinson believes that they are concerned with the movement of fluids in the large bowel. The anatomic confinement of the appendices epiploicæ to the colon where fluids are reabsorbed makes this theory quite probable. He pointed out the dissimilarity between the structure of these processes and the great omentum as a refutal of the protective theory which is held by some authors. The fact that these structures have been found adherent to other inflamed abdominal viscera is not adequate proof of their protective nature. Patterson has suggested that they may act simply as bumpers for the large intestine, fending it from the parieties and other viscera, thus facilitating peristalsis.

Their pathologic changes are chiefly due to mechanical interference with the blood supply or inflammation. Torsion, either within the abdomen or within a hernial sac, is the most frequent cause of disturbed blood supply. Simple incarceration of an appendix epiploica within a hernial sac may be sufficient to cause gangrene. Inflammatory reactions in the form of fat necrosis, subperitoneal hemorrhages and gangrene usually follow a disturbance of blood supply. As a result of sudden torsion the appendix epiploica may become detached, forming a free foreign body within the peritoneal cavity, or it may become calcified remaining attached or becoming detached. Bacterial invasion leading to pure inflammatory changes may occur from an associated diverticulitis. Intestinal obstruction has been produced by adherent bands formed following disease of the appendices epiploicæ. Local peritoneal abscesses and general

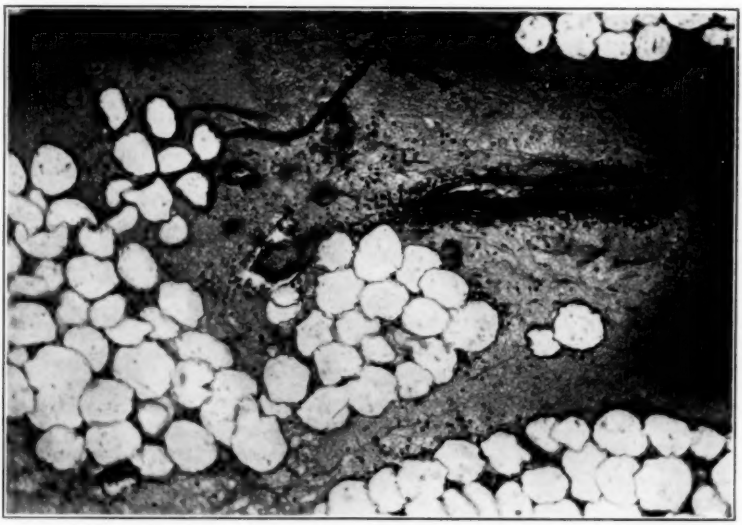

FIG. 1.—Appendix epiploica showing partial thrombosis of central vessel with perivascular leukocytic infiltration. Note the hemorrhage throughout the tissue.

peritonitis have been attributed to disease of the appendices epiploicæ.

Of the pathologic changes occurring in the appendices epiploicæ, intraäbdominal torsion and inflammation are the most common. All cases reported as torsion within a hernial sac and as loose foreign bodies within the peritoneal cavity have been omitted in this paper.

Review of the Cases Reported in the Literature. The first 16 cases of intraäbdominal torsion of the appendices epiploicæ were abstracted and reported by Hunt in 1919. Since no additional cases were found these cases were not included in our tabulation but have been referred to by number in the bibliography, the case number and bibliography number corresponding.

Report of Two Cases. Case 43 (24014). A female, aged 42, was admitted to this hospital, service of Dr. W. Wayne Babcock. Three days before, she was seized with sharp pain in the lower left abdomen, following an attack of coughing. The pain became dull, constant and was made worse by motion. Vomiting occurred for the first and only time after eating dinner the night before admission. The bowels were moved for the first time, since the onset of pain, the night before admission by an enema, this increasing the pain. There were no previous attacks. The appendix vermiformis had been removed 22 years ago. Ten years ago she had an operation for a ruptured ectopic pregnancy. The temperature was 99° F., the pulse rate 90. The abdomen was somewhat obese but not rigid or distended. A deep-lying, tender, nodular, mass the size of a bean was palpated about mid-way between the left anterior superior spine and the umbilicus. The leukocyte count was 11,700 with 75% neutrophils. A pre-operative diagnosis of torsion of an appendix epiploica was made by Dr. Babcock.

Under spinal anesthesia the abdomen was opened through a 10 cm. left transverse muscle-splitting incision. Arising from the sigmoid an appendix epiploica measuring 18 by 30 by 10 mm., purple-red in color, was found and removed by ligation of the base. There was no torsion of the pedicle. The surrounding peritoneum was injected and covered with plastic exudate. Adjacent non-inflamed diverticula of the sigmoid were observed. Pathologic report was acute inflammation, thrombosis and hemorrhage of an appendix epiploica (Fig. 1).

The patient was discharged in 13 days. Until the present, 14 months later, there have been no abdominal symptoms.

Case 44. A male, aged 27, was admitted to the service of Dr. Babcock. He complained of pain, increased by motion, in the left lower abdomen, of gradual increasing severity and of 24 hours' duration. There was no nausea or vomiting. The bowels were moved by an enema at the onset of the pain and moved normally the day of admission. Four months previous he was in the hospital complaining of generalized abdominal pain associated with nausea and vomiting. The diagnosis of subsiding appendicitis or gastroenteritis was made, and he was discharged in a few days. Otherwise there was no history of previous abdominal symptoms. The patient was well developed. There was tenderness on slight pressure in the lower left quadrant, no masses or abdominal rigidity. Rectal examination produced pain and tenderness above and to the left of the prostate gland. The leukocyte count was 9800 with 70% neutrophils. A pre-operative diagnosis of diverticulitis was made.

The abdomen was opened through a 10 cm. transverse muscle-splitting incision mid-way between the left anterior superior spine and the umbilicus.

TABLE 1.—ABSTRACTS OF CASES OF INTRA-ABDOMINAL TORSION SINCE 1919.

Case No.	Sex and age.	Symptoms.				Pre-operative diagnosis.	Origin of diseased appendix epiploica.	Comments.
		Pain.	Duration.		Miscellaneous.			
		Location.	Acute.	Chronic.				
17	F. 35	R. L. Q.	2 days	10 mos.	T. and R. right rectus, obese	Acute appendicitis	Ascending colon	Incidental appendectomy.
18	F. 51	L. L. Q.	3 days	2 yrs.	T. and R. left rectus, mass	Twisted ovarian cystoma	Sigmoid	Turbid peritoneal fluid, plastic exudate.
19	M. 60	L. L. Q.	4 days	....	T. L. L. Q., indefinite mass	Acute appendicitis, left	Lower descending colon	Edema peritoneum; gangrene of appendix epiploicæ.
20	M.	R. L. Q.	....	....	N. and V. 2 attacks in 4 weeks	Acute appendicitis	Cecum	Incidental appendectomy.
21	F. 44	L. L. Q.	12 days	....	Symptoms of peritonitis	Degenerated myomata	Sigmoid	Appendectomy, hysterectomy, bilateral salpingo-oöphorectomy, peritonitis.
22*	F. 45	Epigastric	4 hrs.	....	Symptoms due to acute pancreatitis, obese	Peritonitis	Transverse colon	Torsion of appendix epiploica was incidental autopsy finding.
23	M. 45	R. L. Q.	?	....	Tenderness R. L. Q.	Acute appendicitis	?	Twisted appendix epiploica around perforated appendix.
24	F. 39	R. pelvic L. L. Q.	2 days	15 yrs.	T. L. L. Q., tender swelling by vagina, obese	Torsion of ovarian cyst	Sigmoid	Appendectomy.
25	F. 39	R. L. Q.	8 days	....	Tenderness and rigidity. R. L. Q.	Subacute appendicitis	Ascending colon	Caution! Microscopic degenerated fibroma.
26	F. 35	R. L. Q.	2 days	....	T. above Poupart's lig. and rectal	Subacute appendicitis	Cecum	
27	M. 53	R. hypochondrium	36 hrs.	....	Tenderness, obese	Acute appendicitis	Ascending colon	Appendectomy.
28	M. 43	R. L. Q.	5 days	....	Occasional nausea	Acute appendicitis	Sigmoid	Appendectomy. Serous peritonal fluid.
29	M. 54	R. L. Q.	2 days	....	Tenderness and rigidity	?	Ascending colon	
30	F. 33	Lower abdomen	....	Long time	Unable to work on account of pain	?	?	Kinked chr. appendicitis with twisted append. epip. adherent at kink.
31	F. 33	Lower abdomen	Chronic	....	Pain relieved by 2 hours in bed	Recurrent appendicitis	Sigmoid	Multilocular cysts of append. epip. containing clear fluid. Appendectomy.

* See note on Table 2.

TABLE 2.—ABSTRACTS OF CASES OF INTRA-ABDOMINAL TORSION SINCE 1919.

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Case No.	Sex and age.	Symptoms.				Pre-operative diagnosis.	Origin of diseased appendix epiploica.	Comments.
		Pain *	Duration		Miscellaneous.			
		Location.	Acute.	Chronic.				
32	F. 50	Epigastric	3 wks.	....	Diarrhea, vomit, slight disten., tender and mass	?	Sigmoid	Facial erysipelas; postoperatively.
33	F. 51	L. L. Q.	....	5 yrs.	Increasing constipation, 5 yrs.; nausea and occa. pain	?	Sigmoid	Appendectomy.
34	F. 38	L. L. Q.	....	4 yrs.	Pain followed appendectomy; 5 yrs. ago	?	Sigmoid	
35	M. 64	R. L. Q.	4 hrs.	....	Nausea and vomiting; tender	Acute appendicitis	Sigmoid	Descending colon distended.
36	M. ?	L. L. Q.	2 days	....	Nausea; general tympanites; tenderness	Meckel diverticulum divert. sigmoid transposed append.	Sigmoid	No torsion of pedicle. Thrombotic or embolic.
37	F. 52	R. L. Q.	12 hrs.	....	Tend. and sl. rigid., hacking cough, 3 days; obese	Acute appendicitis	Cecum	
38	M. 58	L. L. Q.	2 days	....	Vomit. intermitt., semi-obese; T. and R., tympanites	Intestinal obstruction	Sigmoid	Partial kink of sigmoid due to disease; app. epip.
39	F. 44	....	....	....	Postoperatively symptoms could not be related	.....	Sigmoid	Torsion of app. epip.; incidental finding during hysterectomy.
40	F. 45	L. L. Q.	2 days	....	Obese, tender and rigidity; nausea	Torsion of ovarian cyst. diverticulitis	Sigmoid	Thin blood-stain peritoneal fluid.
41*	M-mid. aged	Abdominal	3–4 days	....	.....	Acute appendicitis, peritonitis	Sigmoid	Median Peritoneal abscess around gang. app. epip.
42	M.	L. L. Q.	?	?	Symptoms similar to those of left-sided appendicitis	?	Sigmoid	

* Death T—Tenderness R—Rigidity LLQ—Left lower quadrant RLQ—Right lower quadrant
Epig.—Epigastrium N—Nausea V—Vomiting.

A twisted blue-black appendix epiploica measuring 2.5 by 2.5 by 7 cm. was found and removed. Three adjacent yellow-gray appendices epiploicæ were resected. The vermiform appendix was not removed. Pathologic section showed hemorrhagic infarction of an appendix epiploica.

Convalescence was complicated by a pansinusitis, cervical adenitis, and muscular pains. Up to the present, 2½ years later, there has been no return of abdominal pain.

Discussion. To the 42 cases of intraäbdominal torsion or infarction of the appendices epiploicæ reported in the literature we have added 2, bringing the total to 44 (23 males, 21 females). For 37 cases the average age was 44.3 years; the oldest 70, the youngest 20. Many authors state that obesity is a predisposing factor, however, it was directly mentioned or implied in only 15 of these cases.

There were no clinical symptoms referable to the diseased appendix epiploica in 5 cases; the condition being found incidentally at autopsy in 2 instances, and during a laparotomy for another condition in 3 cases. Of the remaining 39 cases, 32 presented acute abdominal symptoms necessitating operation, 8 of these cases also had a history of chronic symptoms, in the remaining cases the symptoms were entirely chronic in character. Abdominal pain is the only constant symptom; the character varies from sudden severe to chronic recurrent; in 3 cases it followed coughing or lifting; motion increased the pain in some cases. The pain was located in the lower abdomen in most cases, the left side was involved in 18, the right in 17, and in 2 cases it occurred in the epigastrium. Tenderness localized at the site of pain was recorded in 22 cases. Nausea was present in 10 cases and vomiting occurred in 8. In 7 cases an abdominal tumor was described.

The pathologic changes in all the cases were more or less similar, the appendix epiploica being somewhat enlarged; and blue, black, or purple in color. On section, thrombosis, hemorrhagic infarction, cellular infiltration, and fat necrosis were characteristic. The diseased appendix epiploica arose from the sigmoid in 26 cases, the cecum in 9, the ascending colon in 4, the transverse colon in 2 and the descending colon in 1. Torsion of the pedicle was described in all but 4 of the cases (Randall, Robertson, Ober and ours). Randall thought the lesion in the appendix epiploica was thrombotic or embolic in origin. In our case thrombosis of the central vessel was found on section, and we do not feel that the adjacent non-inflamed or adherent diverticula had any etiologic significance. Localized plastic peritonitis and peritoneal abscess were present in some cases. Intestinal obstruction was caused by the diseased appendix epiploica in 2 cases (Riedel and Hamilton).

A correct pre-operative diagnosis was not made in any of the cases reviewed. The diagnosis of appendicitis in some form was the most frequent error. Among the pre-operative diagnoses made were torsion of ovarian cyst, diverticulitis, tumor of the sigmoid,

tubo-ovarian disease, cholelithiasis, degenerated myomata, intestinal obstruction and paralysis and peritonitis.

There were 5 deaths in the cases reported; in 2 cases the condition was an incidental autopsy finding, 1 having died of cardiac failure and 1 of acute hemorrhagic pancreatitis. In 3, the disease of the appendix epiploica was directly responsible for death. The case reported by Riedel died 1 day after operation from intestinal obstruction caused by a twisted appendix epiploica arising from the cecum and adherent to the middle portion of a coil of mesentery of the small bowel. In the case of Ebner, death occurred on the seventh postoperative day of intestinal paralysis secondary to torsion of an appendix epiploica. Seelye reports a death occurring a few days after operation due to generalized peritonitis following drainage of an abscess caused by a twisted gangrenous appendix epiploica. This is adequate proof that torsion of the appendices epiploicæ is a serious condition which demands recognition and proper treatment.

Conclusions. 1. Intra-abdominal torsion and hemorrhagic infarction of the appendices epiploicæ are definite clinical entities. To the cases found in the literature, 2 are added.

2. The most characteristic clinical symptom was abdominal pain usually occurring over the site of the lesion. There may be associated localized tenderness. Nausea and vomiting were uncommon. A palpable tumor was present in 7 cases.

3. Intra-abdominal disease of the appendices epiploicæ resulted in complications causing death in 3 cases.

4. Pre-operative diagnosis is difficult. In any obscure case of abdominal pain which is not explained by operative findings, an exploration of the appendices epiploicæ should be considered.

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I wish to acknowledge my appreciation to Dr. Babcock for the use of these cases.

CEREBRAL LESIONS IN UNCOMPLICATED FATAL DIABETIC ACIDOSIS.*

By Edward S. Dillon, M.D.,
CHIEF, METABOLIC DIVISION, PHILADELPHIA GENERAL HOSPITAL; ASSISTANT PROFESSOR OF DISEASES OF METABOLISM, GRADUATE SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA,
H. E. Riggs, M.D.,
CHIEF, DIVISION OF NEUROPATHOLOGY, PHILADELPHIA GENERAL HOSPITAL,
AND
W. Wallace Dyer, M.D.,
ASSISTANT CHIEF, METABOLIC DIVISION, PHILADELPHIA GENERAL HOSPITAL, PHILADELPHIA, PA.

(From the Divisions of Metabolic Diseases and Neuropathology of the Laboratories of the Philadelphia General Hospital.)

A diabetic ought not to die from uncomplicated coma. In the first place, barring an infection with sequential acidosis, that he is in coma is presumptive evidence of ignorance or neglect. In the second place, even though coma is present, adequate and early therapy should save the patient. Nevertheless, uncomplicated diabetic coma deaths continue to occur. In a total of 35 coma fatalities from 1923 to 1935 Joslin[5] reported that 11 had no other complications. In our clinic from January 1, 1931 to July 1, 1935, 21 out of 52 coma deaths were uncomplicated. In the series here presented the criterion for coma is a plasma carbon dioxid combining power of 20 vol.% or less, though the difficulty resulting from an arbitrary figure is recognized. Almost all of our 21 cases were not hospitalized until hours after the beginning of the symptoms of oncoming coma.

The clinical picture of these patients in the terminal stages is strikingly similar, the outstanding features being the very low blood pressure, the rapid heart rate and usually a sharp rise in temperature. These features may be present when the patient is admitted but more often appear after the coma treatment has been begun. Not infrequently they are present when good response is obtained to treatment as measured chemically by a rising plasma CO_2. Lande[6] has reported similar findings and found that recovery was rare in the presence of both cardiovascular failure and marked hyperpyrexia.

* Preliminary report given before the Philadelphia Neurological Society, December, 1934.

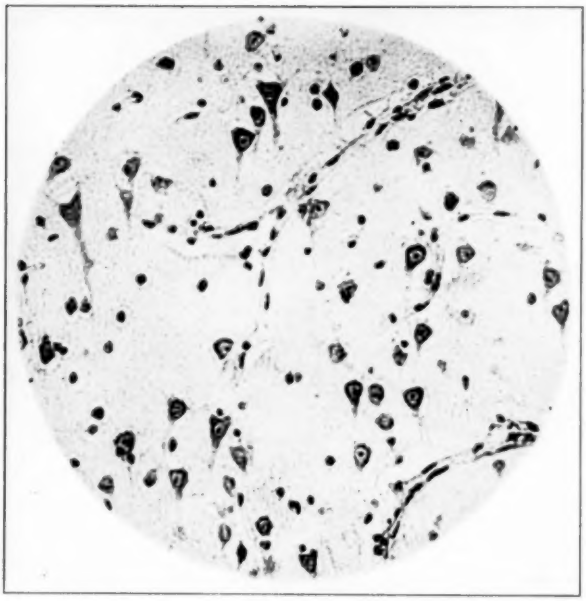

FIG. 1.—Case 3. Cortex showing perivascular and pericellular edema with degenerative changes in capillary endothelium. × 207.

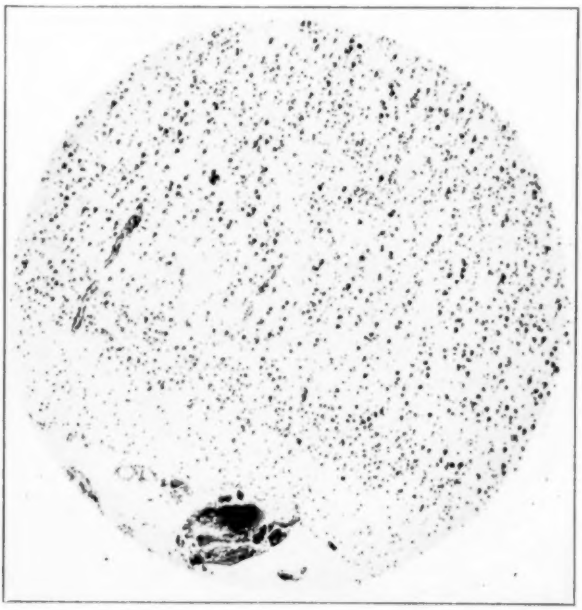

FIG. 2.—Case 7. Cortex showing cellular proliferation of the cortical vessels and focal areas of cell loss in third and fourth cortical layers (Brodmann). × 48.

FIG. 3.—Case 6. Putamen and globus pallidus showing perivascular edema with fibroblasts and macrophages in the dilated perivascular spaces. Vessels show cellular proliferation. × 69.

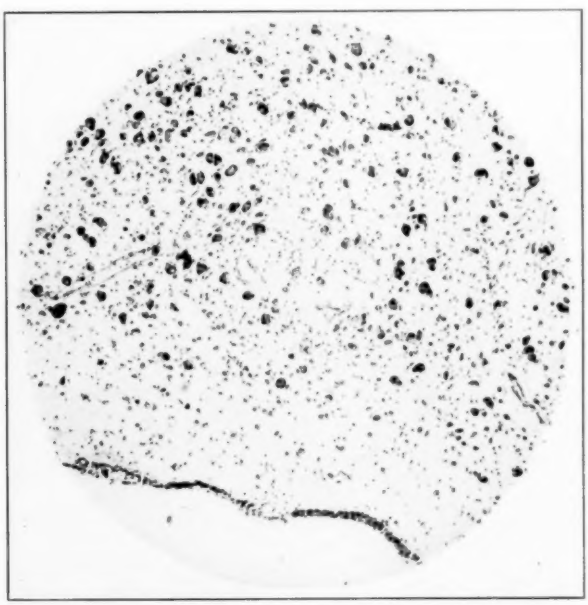

FIG. 4.—Case 3. Paraventricular nucleus of the tuber showing dilatation of the vessels and swelling of the endothelium. There is loss of many of the large hyperchromatic cells. The ependyma is proliferated. × 69.

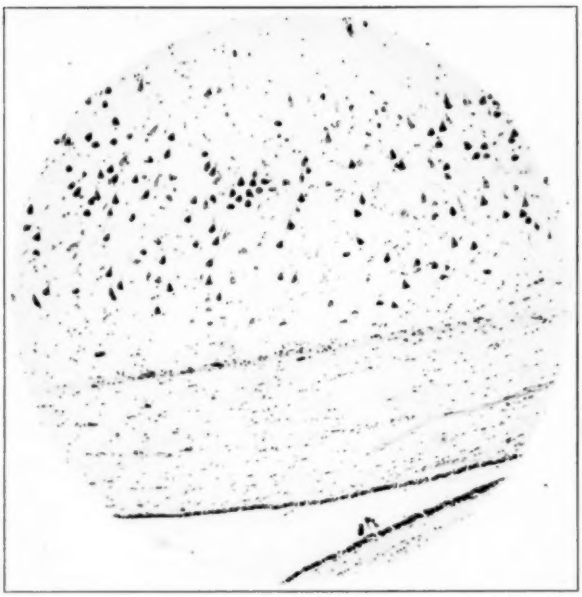

FIG. 5.—Case 5. Sommer's sector of Ammon's horn showing focal cell loss. × 69.

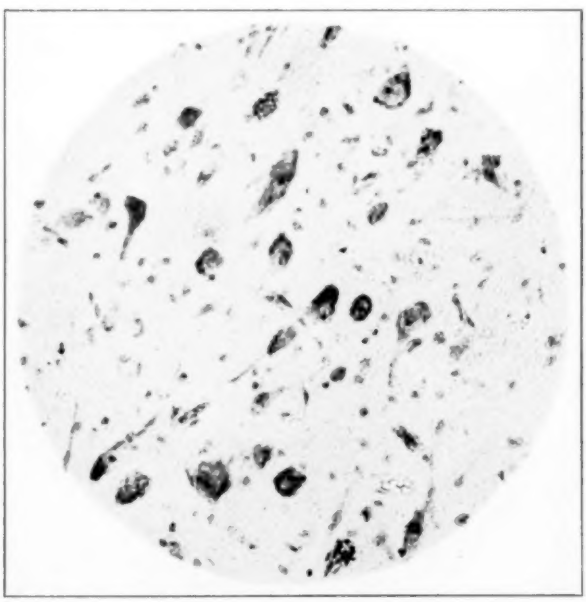

FIG. 6.—Case 2. Dorsal vagus nucleus showing cell degeneration and fragmentation. × 149.

Several investigators have predicted a cerebral factor but to our knowledge no one has demonstrated a cerebral lesion or explained its physiologic modus operandi.

We have studied 8 cases in which no adequate gross pathologic cause of death could be found; all were without demonstrable infection; the diabetes was of comparatively short duration; and the patients were young enough to minimize the usual degenerative vascular changes.

TABLE 1.—SUMMARY OF DATA OF 8 UNCOMPLICATED CASES OF DIABETIC ACIDOSIS.

Case No.	Age, color, sex.	T. P. R. admission.	Final T. P. R.	Admitted.	Hours in hospital.	Duration of diabetes (months).	Mental state on admission.	Acidosis, duration on admission (hours).	Blood findings on admission.					Treatment.				Effects of treatment.	
									Sugar, mg.	CO_2, vol. %	Urea N. mg.	W. B. C., thous.	Hb, gm. %	Insulin, units.	Saline, liters.	Glucose, gm.	Soda, gm.	Sugar, mg.	Rise in CO_2, vol. %
1. J. J.	35 B M	97[a] 128 24	..	1/29/30	8.5	?	SC*	24	1500	24	72	..	..	250	2.5	0	30	720	15
2. C. S.	14 W F	96[b] 110 24	105 ? 34	3/8/31	96	18	SC	72	278	14	14	24.5	17.5	215	2.0	134	40	125	25
3. J. S.	45 W M	99[c] 122 36	106[b] 88 26	9/6/33	23	36	U*	24	748	12	23	14.5	16.0	245	3.0	90	26	242	30
4. K. D.	25 W F	97[b] 90 16	102 110 34	9/20/33	15	?	U	24	770	14	30	29.8	16.5	400	5.0	60	26	380	26
5. J. G.	30 W M	94[a] 140 40	101 102 40	7/17/34	6.5	2	U	72	428	11	..	35.2	14.9	270	4.0	160	14	584	7
6. M. J.	35 W F	101 140 40	106[b] 158 34	8/10/34	10	36	U	48	720	13	30	..	..	400	3.6	290	20	600	9
7. S. J.	38 B M	97[a] 96 32	101 128 20	9/18/34	3	2	U	72	682	10	65	16.3	14.6	270	2.0	0	7	1096	9
8. G. H.	36 B M	102 142 36	107 ? ?	5/16/35	2	3	U	48	1256	18	78	11.8	13.7	160	2.7	0	0	1136	8

* SC = Semiconscious. U = Unconscious.

A summary of certain clinical and chemical data is to be found in the table. Case 1 has been included, although the admission CO_2 was 24, because clinically and pathologically the picture was similar to the other 7 cases and because it stresses the fallibility of creating an arbitrary chemical figure to indicate coma and precoma.

Postmortem examination of the various organs in summary showed varying amounts of myocardial degeneration, congestion and cloudy swelling of the other organs. Our interest, however, was chiefly in the brain, of which detailed studies were made. Autopsies were performed at varying times within 24 hours after

death. All brains were sectioned immediately upon removal and dehydrated in graded alcohols. The tissue was embedded in celloidin and stained with toluidin blue, hematoxylin-eosin, and Van Giesen stains.

Description of Cerebral Lesions. In cases of diabetic acidosis, the subarachnoid space is moderately widened, the veins show dilatation and stasis with escape of both serum and cellular contents. The endothelial cells of the arachnoid are proliferated. Collagen fibers and young fibroblasts are present, as well as macrophages filled with blood pigment.

In the cortex, the capillary bed is dilated and shows degenerative changes in the endothelial cells. The small cortical vessels show similar changes with, additionally, the increase of the adventitial cells. There is perivascular edema and often masses of blood pigment in the perivascular space.

The cellular architecture is disturbed by the loss of ganglion cells, especially in foci in the third and fourth layers (Brodmann). The ganglion cells, themselves, show pericellular edema, with shrinkage of the cell. The cytoplasm is shrunken, and the Nissl substance greatly reduced. The processes are pale, spikelike and often detached. The nucleus is large and granular in appearance. The nucleolus is at one pole, and is often fragmented. In the lower layers, the cytoplasm finally disappears to leave a bare, dark, nucleus with a fragmented nucleolus. There are many shadow cells and bits of cellular débris. In cases which have been in coma several days, there is accumulation of lipoids in the cells and some of the ganglion cells show sclerosis.

The cortical neuroglia is not greatly increased, although satellitosis is present and the astrocytes show small masses of yellow pigment in the cytoplasm. However, around the ventricles there is proliferation of the subependymal astroglia and the ependymal lining of the ventricles is increased with the formation of wartlike projections, especially in the hypothalamic portion of the third ventricle.

In the choroid plexus, the vessels in the tufts show extreme stasis with degenerative changes in the walls, and collagen fibers filling the space between the vessels and the epithelial layer. The epithelial cells themselves show a swollen, granular cytoplasm, and pyknotic nucleus. Many are desquamated.

In the basal ganglia the vascular changes are more intense than in the cortex. Here the dilated perivascular spaces often contain collagen fibers, fibroblasts, and occasional macrophages filled with blood pigment. This is most marked in the large subependymal veins. The effects of this tissue edema vary greatly in the basal nuclei. All the ganglion cells show acute degenerative changes, but in the globus pallidus the cells are reduced to mere shadows, often with lipoid accumulation. In some of the cases where acidosis was of long duration, the vessels of this nucleus are infiltrated with

calcium salts. The cells of the substantia nigra are, for most part, reduced to masses of pigment.

The large hyperchromatic cell groups of the hypothalamus are greatly swollen, with an eccentric or partially protruded nucleus. The cell body is irregular with large isolated masses of chromatin deposited at the periphery. Lipoid accumulation is present, especially in the cells of the substantia innominata. Sommer's sector of Ammon's horn shows selective ischemic change with loss of cells.

The pyramidal pathway shows status spongiosus and great decrease in neuroglial cells. In the cerebellum, the cells of the granular layer are decreased, and the Purkinje cells, which are also reduced, present ischemic cell changes. The dentate nucleus is greatly reduced in size. The cells show a hyalin-like polychromatic cytoplasm with lipoid at one pole. The nucleus is compressed at the other pole and contains a large metachromatic nucleolus.

In the medulla, the changes in the inferior olive parallel those in the dentate nucleus. The dorsal motor nucleus of the vagus shows greater cell degeneration than the other nuclei of the floor of the fourth ventricle. Some of the cells are entirely fragmented, others are covered with melanotic pigment; the capillaries are very numerous and widely dilated and the perivascular edema is marked. The extramedullary roots of the vagus show proliferation of Schwann cells and of perineural connective tissue.

Summary of Pathologic Brain Changes. In brief, the brain in fatal diabetic acidosis shows lesions like those seen in acute asphyxia. The primary pathologic changes occur in the cerebral capillary bed. The capillaries are dilated, and the endothelial cells show degenerative changes with increased permeability of the walls as evidenced by the presence of perivascular and pericellular edema.

As a result of the cerebral edema there is proliferation of neuroglia, especially in the subependymal and marginal areas, and acute degenerative changes in the ganglion cells. The capillary changes are identical throughout the brain, but the degree of cellular destruction varies in different localities. The degeneration of the ganglion cells is greatest in the third and fourth cortical layers, in the extrapyramidal system, in the cerebral vegetative centers of the diencephalon and of the medulla, in the olivocerebellar system and in Sommer's sector of Ammon's horn. Because of its structural makeup, the choroid plexus is severely damaged.

Discussion. At present, we have no exact knowledge of the mechanism of production of the cerebral anoxia in diabetic acidosis. However, relying upon the results of experimental investigators, we have attempted a theoretical reconstruction of the abnormal physiology. We feel that there is cerebral anoxia, primarily based upon reduced blood volume with hemoconcentration.[1] As the result, there is marked reduction in blood pressure both systolic and dias-

tolic. This causes a reduced cerebral blood flow since it has been shown that cerebral blood flow passively follows changes in blood pressure.[11]

Due to the absence of a vasoconstrictor mechanism in the intracerebral vascular bed,[12] stasis occurs more rapidly in the brain than in other portions of the body and leads to local anoxia of the capillary wall.[7] This anoxia is further increased by the inability of concentrated blood to take up oxygen as readily as normal blood.[9] Due to these factors there is an increased permeability of the capillary wall.

The increased permeability occasions cerebral edema. Once the edema is established rapid death of the cells takes place due to their intolerance of stagnant tissue fluids,[3] and their high oxygen requirements.[2,4,8]

A variation in the susceptibility of parts of the brain to anoxia has been demonstrated in the work carried out by the U. S. Bureau of Mines, relative to the effect of atmosphere deficient in oxygen.[10] In these reports the areas of the brain indicated by Chornyak as most susceptible to oxygen insufficiency are identical with those in our cases which show the greatest damage.

It will thus be seen that the reduced blood volume and hemoconcentration with resulting low blood pressure produces vascular stasis more marked in the brain than elsewhere. This, in turn, results in increased capillary permeability, transudation of fluid, pericellular edema and cellular death. It might be argued that these cerebral vascular changes are due to capillary damage by the increased acid bodies found in coma. If the lesions were specific for diabetic coma such a theory would certainly be tenable, but they are not specific for diabetic coma. Similar cerebral changes have been found here in non-diabetics of at least two types; 1, Those patients which have had an acute exsanguinating hemorrhage, and 2, cases dying from congestive heart failure. In diabetic coma, there is a reduction in total blood volume comparable to a severe hemorrhage. Electrocardiographic and pathologic evidence frequently point to severe myocardial damage associated with diabetic coma. It is our belief that the cerebral vascular stasis is initiated by the reduced blood volume, which stasis is subsequently increased as a result of myocardial failure.

We have postulated the possibility, that the cerebral lesions may be due to circulatory cerebral decompensation. It is our belief that when the cerebral lesions become irreversible, due to long continued cellular anoxia, they further embarrass cardiac function, by paralysis of the vasomotor and other vegetative centers, so that in spite of an improvement in the acid base balance, the patient dies from vasomotor collapse or from failure of respiratory or cardiac function. We are not prepared to attempt an explanation of the terminal hyperpyrexia. It is possible that it is central in origin

resulting from degenerative changes produced in the region of the hypothalamus.

Summary. 1. The clinical and chemical findings in 8, fatal, uncomplicated, cases of diabetic acidosis have been described.

2. The pathologic brain findings in these cases have been reviewed.

3. A theory for the failure of adequate treatment to produce recovery in these cases has been advanced.

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A CASE OF CAROTENEMIA AND DIABETES MELLITUS WITH NECROPSY REPORT AND ANALYSES OF LIVER FOR CAROTENE, VITAMIN A, TOTAL FAT AND CHOLESTEROL.

By Arthur C. Pariente, M.D.,

ASSISTANT IN MEDICINE, NEW YORK UNIVERSITY COLLEGE OF MEDICINE; ADJUNCT ASSISTANT VISITING PHYSICIAN, THIRD (NEW YORK UNIVERSITY) MEDICAL DIVISION, BELLEVUE HOSPITAL; LEDERLE RESEARCH FELLOW IN MEDICINE,

Clara H. Present, M.A.,

RESEARCH FELLOW IN MEDICINE, NEW YORK UNIVERSITY COLLEGE OF MEDICINE, NEW YORK,

AND

Elaine P. Ralli, M.D.,

ASSISTANT PROFESSOR OF MEDICINE, NEW YORK UNIVERSITY COLLEGE OF MEDICINE; ASSOCIATE VISITING PHYSICIAN, THIRD (NEW YORK UNIVERSITY) MEDICAL DIVISION, BELLEVUE HOSPITAL.

(From The Third (New York University) Medical Division, Bellevue Hospital, and the Department of Medicine, New York University College of Medicine.)

The syndrome known as carotenemia has long been recognized and its frequent incidence in patients with diabetes mellitus noted.[1,2,3] There is however only 1 case[4] in the literature which

includes a necropsy report. Because of this, and the recent interest in carotene as a precursor of vitamin A, we are reporting the clinical course and postmortem findings of a diabetic patient with carotenemia.

Wachenroder,[5] in 1826, isolated a yellow pigment from carrots and named it carotin. In 1896, Baelz[6] described a condition of pigmentation of the skin which he called aurantiasis cutis. This was due to the ingestion of mikan, a Japanese orange. In 1903, Crocker[7] noted that "there is a xanthochromia of the skin not due to jaundice in some cases. It is more marked on the face and trunk than on the limbs, but the conjunctivæ and buccal mucous membrane are uncolored and there is no bile in the urine and feces." Although he did not state the cause, it is probable that his description referred to cases of carotenemia. The first case in a diabetic patient was described by von Noorden,[8] in 1904, as xanthosis diabetica. It was characterized by a canary-yellow tint of the palms, soles, and nasolabial folds. He regarded a high vegetable diet as responsible and found that when the diet was discontinued the yellow color disappeared more rapidly in normals than in diabetics. Moro[9] later described "sub-icterus" in nurslings fed on carrots and milk. Following this van den Bergh and Snapper,[1] in 1913, showed that the pigmentation in diabetic xanthosis was due to a pigment of the nature of a vegetable lipochrome. Burger and Reinhardt[10,11] believed that the pigment was exogenous in orgin and demonstrated a rise in serum carotene after a diet of green vegetables. Palmer and Eckles[12] had previously stated that the carotene of milk fat was not synthetized in the body, but was exogenous. The first description in English was by Hess and Myers.[13] They noted coloration of the skin in infants on a diet containing carrots. Since then numerous cases have been reported.

The dietary substances thus far listed as causing carotenemia are: carrots, pumpkin, yellow squash, yellow turnip, parsnip, spinach, green and yellow beans, kale, orange, and eggs.

Physiologic Chemistry. The vegetable pigment carotene is a highly unsaturated hydrocarbon with the formula $C^{40}H^{56}$. There are three natural isomers: the α, β, and γ forms. In spite of considerable investigation within the past few years, the fate of ingested carotene is still open to discussion. Ahmad[14] found that on a fat-free diet rats excreted 90% of the carotene fed, but there was almost complete absorption when the diet contained 10% fat. Greaves and Schmidt[15] found that in rats the absorption of β-carotene is largely dependent on the presence of bile acids. According to Drummond,[16] carotene may be absorbed from the intestines in the form of a water soluble, diffusible complex with bile acids. In the blood a double colloidal phenomenon is involved (Palmer[17]). First there is a colloidal adsorption of carotene by albumin and second a colloidal solution of the albumin in plasma. This theory was

based on the fact that carotene could not be extracted directly from plasma. This has since been partly contradicted by van den Bergh and Muller[18] who found that a colloidal aqueous solution of carotene will act similarly.

That carotene is converted to vitamin A and will cure the symptoms of A deficiency has been shown by Moore[19] and others. The chemistry of this conversion is apparently a hydration of the central double bond of the carotene molecule—

$$\underset{\text{Carotene}}{C_{40}H_{56}} + 2H_2O \longrightarrow \underset{\text{Vitamin A}}{2C_{20}H_{30}O}$$

The α, β, and γ isomers have the values 1–2–1 as sources of vitamin A. The actual mechanism of the conversion is unknown. Some workers have suggested an enzyme in the liver,[20,21] but other workers have been unable to confirm these results.[22]

Carotene in excess of the amount which the liver is capable of converting to vitamin A is either destroyed or excreted. Although both Hess and Myers[13] and Wells and Hedenburg[23] reported that after carotene injection the urine became a darker yellow, it is probable that the deeper color was due to impurities in the carotene resulting from the method of extraction rather than to carotene itself. Palmer[24] found carotene in human milk fat. De Buys[25] reported the case of a mother on a high vegetable diet whose milk was a deep orange color and whose children were born pigmented and remained so until after weaning. Carotene has also been demonstrated in cerumen.[26]

The chief means of excretion is apparently through the sweat. Miyake[27] stated that in cases of carotenemia the pigment was distributed around the sweat pores, and that the sweat gland apparatus was more intensely pigmented than other skin structures. Experimentally, Ansai[28] found that in rats the pigment was excreted in the sweat and then absorbed by the horny layer of the skin. The horny layer is thickest on the palms and soles, which are usually the most pigmented parts of the skin in carotenemia.

We are reporting the clinical course and postmortem findings of a diabetic patient who developed carotenemia and later died of acute intestinal obstruction:

Case Report. B. R., a single white male, aged 45, laborer by occupation, was first admitted to the wards of this hospital on January 29, 1934. His family history was significant in that his father had died of diabetes mellitus at the age of 74. His only previous disease was measles in childhood. Although he had lost 50 pounds in the preceding year, his complaints of polydipsia, polyuria, and polyphagia had been present only 1 month. Physical examination revealed an emaciated, weak, listless male, weighing 115 pounds. There was a pronounced acetone odor to the breath but no hyperpnea. He was dehydrated. The heart sounds were normal, rate 80, rhythm regular with occasional premature contractions. The blood pressure was 154/108. The blood count was within normal limits. The urine on

admission was colorless, specific gravity 1.030, glucose 3.5%, acetone and diacetic acid marked. The patient was treated with insulin and infusions of glucose and saline and was acetone-free in 8 hours with a blood sugar of 160 mg. % after having received 290 units of insulin, 300 gm. of glucose, and 4 liters of a normal saline solution. His diet and insulin requirement were then adjusted and he was discharged on March 20, 1934, on a diet of carbohydrate 200 gm., protein 75 gm. and fat 85 gm. and 30 units of insulin daily.

He attended the clinic irregularly and re-entered the hospital on July 26, 1934, with a history of having omitted insulin and broken his diet for 1 month. His weight had decreased 94½ pounds. His urine contained glucose and ketone bodies. He was again readjusted as to diet and insulin, his weight increased to 110 pounds, and he was discharged on August 30, 1934, on a diet of carbohydrate 300 gm., protein 105 gm. and fat 118 gm., with 30 units of insulin daily.

He again failed to attend the clinic regularly and re-entered the hospital on November 21, 1934, weighing 91 pounds, in mild ketosis and with nutritional edema. He was given a diet of carbohydrate 300 gm., protein 70 gm. and fat 85 gm., with 80 units of insulin daily. In addition, carotene was given as a source of vitamin A. Before the administration of carotene his blood serum carotene averaged 0.242 mg. % (method of White and Gordon[29]). He received a total of 255 cc. of a 0.3% solution of carotene in oil over a period of 62 days. At the end of this time the serum carotene had risen to 0.688 mg. %. After 41 days, with a serum carotene of 0.540 mg. % the palms of the hands and soles of the feet became yellow and there was a faint diffuse pigmentation of the head. This coloration persisted during the whole period of observation, which extended up to 2 weeks after the cessation of carotene administration. He was discharged on May 2, 1935, in excellent physical condition, being sugar and acetone free and having gained 34 pounds.

He was brought into the hospital on May 6, 1935, in a stuporous state, acutely ill, in shock, and in marked ketosis. The abdomen was rigid. The urine contained glucose, acetone and diacetic acid; the blood sugar was 500 mg. %; the CO_2 combining power was 8 volumes %; and the blood non-protein nitrogen was 100 mg. %. The white blood count was 46,100 with 85% neutrophils. He was treated with insulin and infusion and clyses of glucose and normal saline, and received a transfusion of 500 cc. of whole blood. In 14 hours his urine was acetone-free; the blood sugar was 143 and the N.P.N. 75 mg. %; the CO_2 combining power was 35 volumes %. His condition was greatly improved. The white blood count had fallen to 10,150 with 86% neutrophils. However, his abdomen was still rigid and distended. The patient now vomited for the first time, and the vomitus gave a markedly positive benzidin reaction. The temperature had risen to 102° F. A diagnosis of intestinal obstruction was made and laparotomy advised.

At operation the obstruction was found to be due to a Meckel's diverticulum and a Mickulicz ileostomy was performed. The patient died 9 hours postoperatively.

Autopsy (48 hours postmortem). We are indebted to the Pathological Laboratories of Bellevue Hospital for the autopsy report. The positive findings were: Adhesions about a Meckel's diverticulum with localized peritonitis. Immediately above the aortic ring and extending for several centimeters were small, irregular, raised areas, 2 to 4 mm. in diameter. These plaques were a deep orange-yellow color except for small yellowish-white centers. The intima for the most part was normal. In the abdominal, and to a lesser extent in the thoracic aorta, were many similar small plaques relatively isolated. The superior mesenteric artery presented an unobstructed lumen in its proximal portion with several non-elevated orange-

yellow intimal plaques. About 2½ cm. from the origin of this artery, there was one plaque measuring 2 cm. in length, ¾ cm. in width, and 3 to 4 mm. in depth. The proximal portion of this plaque was covered by endothelium but the distal half presented a tapering extremity which projected freely into the lumen of the vessel, unattached to the underlying intima.

The liver weighed 1800 gm. and showed fatty changes. The fat in the mesentery of the small intestine exhibited many irregular sharply defined areas colored orange-yellow in contrast to the surrounding light yellow of the normal fat. This change was limited to the fat of the mesentery of the small intestine and was not present in the retroperitoneal or subcutaneous fat.

Microscopically the liver showed no abnormal pigmentation. Fat globules were present in about 80% of the polygonal cells. The cytoplasm of many cells showed vacuolated areas which did not stain with Sudan III. Glycogen was present only in small amounts as determined with Best's carmine stain.

Section through the large plaque in the superior mesenteric artery revealed a large intimal plaque lying in a trough formed by a wavelike depression of the media and adventitia. The plaque consisted of a superficial portion of dense connective tissue and a deeper vacuolated area containing many acicular spaces. Fat stains revealed extensive fat deposits in the deeper half of the plaque.

The liver was analyzed for vitamin A by the method of Davies[30] and for carotene by colorimetric comparison against Lovibond yellow glasses. Table 1 shows the content of vitamin A and carotene as compared to findings in other cases. Table 2 gives the liver fat in this case.

TABLE 1.—ANALYSIS OF LIVER FOR VITAMIN A AND CAROTENE IN CASES OF DIABETIC AND NON-DIABETIC INDIVIDUALS AS REPORTED BY OTHER OBSERVERS AND IN THIS CASE.

(Lovibond Blue Units Represent Vitamin A; Lovibond Yellow Units Represent Carotene).

A. Blue units per gram of liver tissue:

	Moore.[31]	Wolff.[32]	Ralli.[33]	This case.
Diabetes mellitus	1160	484	414	1317
Non-diabetic	282	206–245	356	

B. Yellow units per gram of liver tissue:

	Ralli.[33]	This case.
Diabetes mellitus	29.9	39.2
Non-diabetics	10.1	

TABLE 2.—LIVER FAT AND CHOLESTEROL.

Total lipid* gm. %	11.700
Unsaponifiable fraction gm. %	0.552
Total cholesterol† gm. %	0.296
Cholesterol esters gm. %	0.088
Free cholesterol gm. %	0.208

* The total lipid and unsaponifiable fractions were determined on an alcohol-ether extract of the wet tissue—the total lipid being the petroleum ether soluble fraction.

† The micro-gravimetric method of Man and Peters[34] was modified for application to tissue lipids.

Discussion. Gordon, Connor and Rabinowitch[4] reported the postmortem findings in a diabetic who had had a yellow-colored skin for 14 years. At autopsy the vertebral arteries contained large golden yellow nodules. The arteries of the circle of Willis showed a

severe degree of arteriosclerosis and were a bright yellow color. Microscopic examination of these vessels showed changes similar to those observed in our patient. Our case, in addition, had yellowish deposits in the mesenteric fat.

The occurrence of a high blood carotene in diabetics has been reported by Brandaleone and Ralli.[3] They found the average fasting level in normals .109 mg. % and in diabetics .262 mg. %. The source of this increased blood carotene is a matter of speculation. Palmer[35] has said that "even a diabetic could not show a xanthosis unless his diet contained carotinoids." Another explanation for the increase in blood carotene in diabetics has been suggested by previous investigations from these laboratories.[33] This explanation points to the possibility of an interference in the conversion of carotene to vitamin A by the liver. In the analyses of the livers of 8 diabetics and 13 non-diabetics[33] for vitamin A and carotene, it was found that the carotene content was higher in the diabetic individuals. If ingested carotene accumulates in the liver, due to a diminished ability on the part of that organ to convert it to vitamin A, a rise in blood carotene might result because of the consequent inability of this organ to absorb as much carotene from the blood. Another explanation for the accumulation of carotene in the liver might be a failure to destroy the pigment. To a certain extent the pigment is destroyed in the body, but there is no proof of where this destruction takes place.

Rabinowitch[2] found a high blood carotene associated with an increase in blood cholesterol in diabetics. The figures of other workers[33] do not entirely confirm this and Boeck and Yater[36] found no relation between xanthosis and blood fat. It might be, however, that since carotene is handled by the body in much the same manner as the fats, that with a disturbance of the metabolism of carotene the excess would be found in the fat deposits. The orange-colored deposits in the mesenteric fat observed in this case and the intensely yellow color of the arterial plaques in both cases support this suggestion.

Summary. The case of a 45-year-old white male with a history of diabetes mellitus of 2 years' duration is reported. Prior to the administration of carotene the blood carotene was higher than normal. Following the administration it rose to a level of .540 mg. % and at this level clinical evidence of carotenemia was observed. Postmortem examination revealed deposits of carotene in the mesenteric fat and in the arterial plaques.

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ARTERIOSCLEROSIS IN YOUNG DIABETICS.

A Method for Its Recognition by Arterial Elasticity Measurements.

By Phillip Hallock, M.D., M.S.,
MINNEAPOLIS, MINN.

(From the Department of Medicine and Graduate School, University of Minnesota.)

It is a commonly accepted clinical observation that the peripheral arteries of diabetics are more susceptible to the development of arteriosclerosis than are those of non-diabetics. This observation has been confirmed by the finding of extreme sclerotic changes in vessels of extremities amputated for diabetic gangrene and by the visualization of peripheral arterial calcification by Roentgen ray.

Autopsy studies show further that approximately 100% of diabetics dying after 40 years of age have some evidence of vascular sclerosis, and that at least 50% of all diabetics die as a result of cardiovascular complications. The high incidence of cardiovascular disease can be explained by modern advances in treatment and improvement in dietary régime whereby the life of the diabetic is definitely prolonged, or, as a writer on the subject has recently stated, "the diabetic now lives long enough to develop cardiovascular disease."

It is interesting then, to inquire when arteriosclerosis has its inception in the life of the diabetic. Does it manifest itself early in the course of the disease, irrespective of the age of the diabetic, or does it appear only as a late manifestation particularly in older diabetics who are already in the arteriosclerotic age? A knowledge, therefore, of these factors is extremely important, because if the span of life of the diabetic is to approach that of the normal, premature arteriosclerosis much be prevented. On the other hand, if arteriosclerosis is already present, the management of the patient should be such as to prevent, if possible, further development of the degenerative process.

Recent work indicates, not only that arteriosclerosis is a common complication in the elderly diabetic, but also that it may develop prematurely in young diabetics. This has been ascertained by various procedures. Warren,[2] in a study of 72 autopsies upon diabetics of 40 years of age and under, noted tissue changes secondary to arteriosclerosis in 50% of the cases. Joslin[3] and Shepardson,[4] separately, found by Roentgen ray examination, a relatively high incidence of vascular sclerosis in the lower extremities of a large number of young diabetics. Further confirmation of the existence of premature arteriosclerosis in young diabetics has recently been established by Rabinowitch, Ritchie and McKee,[1] who studied by statistical methods the relationship of cardiovascular disease to the age of diabetics and to the duration of the disease. In compiling their data, not only did they employ the Roentgen ray technique for studying calcification of the bloodvessels of the lower extremities but also they searched for evidence of arteriosclerosis by examining the retinal vessels, by determining roentgengraphically the size of the cardiac shadow, and by utilizing other clinical procedures, *e. g.*, blood-pressure determinations, palpation of the radial vessels and auscultation of the heart sounds.

The problem of arteriosclerosis may also be investigated by measuring the degree of vascular sclerosis in terms of arterial elasticity or arterial rigidity. For the purpose of this study I recorded the elasticity of bloodvessels in 22 diabetics, all of whom were under 35 years (Table 1); 18 were 20 years and under; the youngest diabetic recorded was 6 years of age (average, 16 years). The duration of the diabetes ranged from 3 months to 6 years, with the exception

of 1 case in which the patient gave the history of having had the disease for a period of 8 years (average about 3 years). All were receiving insulin and could be classified as moderately severe diabetics with one exception in which the condition was mild. Two had been admitted to the hospital on 3 different occasions, each time in a state of diabetic coma. The blood pressure readings in all cases were normal.

TABLE 1.—ARTERIAL PULSE WAVE VELOCITIES IN DIABETES.

No. of cases.	Age.	Sex.	Radial pulse wave velocity (meters per sec.).	Aortic pulse wave velocity (meters per sec.).	Duration of diabetes.
1	6	M	5.5	..	3 years
2	10	F	6.15	4.64	5 years
3	10	F	5.43	5.26	2 years
4	11	M	5.7	..	1 year
5	11	M	6.0	4.0	2 years
6	12	F	5.52	4.05	2 years
7	12	F	5.7	4.3	5 years
8	13	F	7.0	5.1	2½ years
9	14	F	6.6	6.0	3 years
10	14	M	7.96	5.03	3 years
11	15	F	7.1	6.2	4 years
12	16	M	6.45	4.7	4 years
13	17	M	7.1	4.1	5 months
14	17	M	6.44	4.85	6 years
15	17	M	6.32	4.39	¼ year
16	17	F	9.04	5.16	5 years
17	18	M	6.04	..	¼ year
18	20	M	..	5.6	8 years
19	22	F	6.08	..	¾ year
20	26	M	6.3	..	1 month
21	27	F	6.42	5.45	4 years
22	34	M	8.3	6.89	5 years

In a previous communication, I[5] pointed out that arterial elasticity or arterial rigidity can be evaluated by determining the rate at which the pulse wave is propagated through the arterial tree, inasmuch as it is not possible to measure arterial elasticity directly on the living subject. Since the velocity with which the pulse is transmitted along arteries depends on the elasticity of the vessel walls, one can obtain an index of the degree of arterial rigidity or arterial elasticity by determining directly the velocity of the pulse wave in living man. Bramwell and Hill,[6] after mathematical treatment of the equation relating the velocity at the front of the pulse wave to the coefficient of volume elasticity, have shown that the velocity of the pulse wave is a direct function of arterial rigidity, or an inverse function of arterial elasticity. Thus an increase of velocity of the pulse wave implies an increase in arterial rigidity, or, conversely, a decrease of arterial elasticity. By the employment of an optical recording apparatus I[5] studied the velocity of the pulse wave through the aorta and iliac vessels (velocity of the aortic pulse wave) and through the brachial, radial and carotid vessels (velocity of the radial pulse wave) in a series of 553 normal cases, and was

thus able to establish a mean normal pulse-wave velocity value for various age groups ranging from childhood to old age.

The mean normal pulse-wave velocity values for the various age groups are graphically represented in Figures 1 (velocity of the radial pulse wave) and 2 (velocity of the aortic pulse wave) in the form of point-to-point curves for 5- and 10-year intervals (center line). The outer lines were drawn according to one standard deviation above and below the mean pulse-wave velocity for each age period. Hence, by the definition of the standard deviation, 16% of the normal cases should fall above the upper line and 34% between the upper and center line. It is therefore possible, by plotting

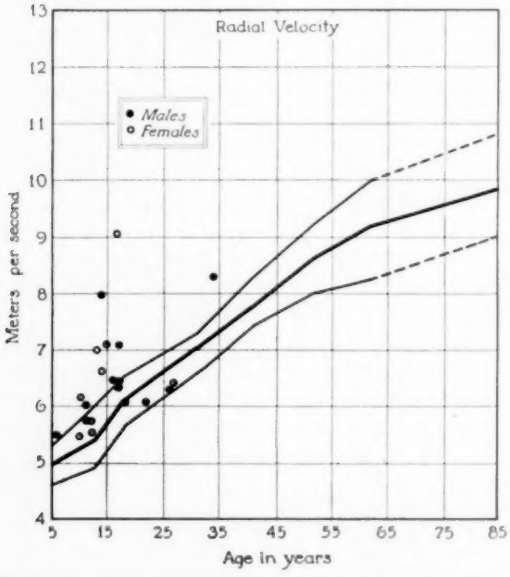

FIG. 1.—Velocity of the radial pulse wave. Graph showing the mean normal curve (center line) and the normal zones of variability (drawn according to one standard deviation above and below the normal mean). The dots indicate the velocity of the radial pulse wave (expressed in meters per second) of 21 young diabetics.

values for velocity of pulse waves on these normal standards, to evaluate the effect of various vascular pathologic states upon arterial elasticity. When the radial velocities for the 21 cases of diabetes were plotted on the standard graph (Fig. 1) 12 cases fell above the upper line where only 3 were expected, 9 fell between the upper and lower line where 14 were expected and none fell below the lower line where 3 were expected. According to the Chi-square test[7] such discrepancies in the velocity of the radial pulse wave could not occur by chance alone oftener than 6 times in 100,000. In view of this significant value it follows that young diabetics as a group have a higher radial pulse-wave velocity than the normal.

On the other hand when the aortic velocities for 17 cases were plotted on the standard graph (Fig. 2) 6 cases fell above the upper line where about 3 were expected, 9 fell between the center and lower line where about 12 were expected, and only two fell below the lower line where about 3 were expected. According to the Chi-square test such discrepancies could occur through the operation of chance alone 30 times in 100; hence cannot be considered statistically significant. Inasmuch as the trend of these values tends

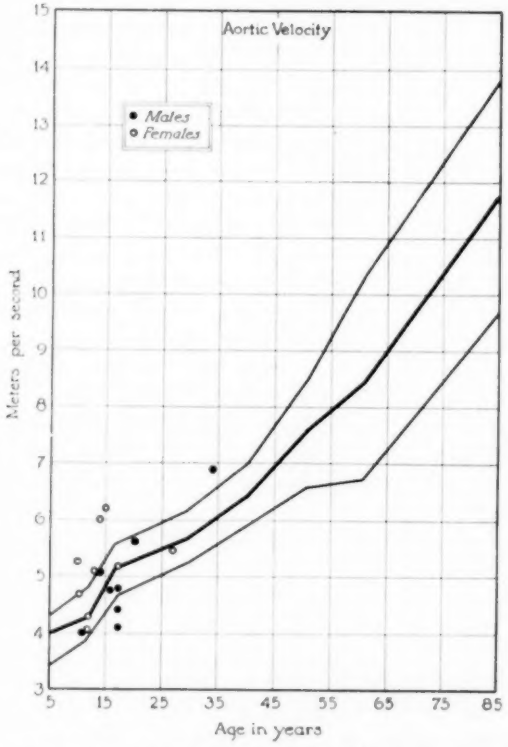

FIG. 2.—Velocity of the aortic pulse wave. Graph showing the mean normal curve (center line) and the normal zones of variability (drawn according to one standard deviation above and below the normal mean). The dots indicate the velocity of the aortic pulse wave (expressed in meters per second) of 17 young diabetics.

toward higher velocities, it is probable that if more cases had been recorded the results would also have been more definitely significant. However, until this can be statistically verified, the effect of diabetes on the elastic arteries such as the aortic and iliac vessels must remain an open question.

Comment. It is apparent from this study that an increase of arterial rigidity or, conversely, a decrease of arterial elasticity in the medium-sized arteries, may accompany the diabetic

state, and that this abnormal decrease of arterial extensibility manifests itself unusually early in the course of the diabetic's life. This is of particular clinical significance when one takes into account the fact that all patients studied in this series have not yet reached the age when arteriosclerotic changes were to be expected. The assumption, must, therefore, be advanced that diabetes predisposes the vascular system, perhaps by some morbid metabolic derangement, to the development of premature arteriosclerosis, and in consequence, stiffening of the arterial wall.

The results of this study are supported by findings of other writers who have investigated the problem by various methods. As already mentioned, Shepardson[4] found by roentgenologic study of arteries of the lower extremities evidence of arteriosclerosis in 36% of 50 diabetics, the average age being 23.4 years and the average duration of the disease being 6.9 years. Joslin[3] by a similar technique found evidence of arteriosclerosis in diabetics 50 years of age and under in 15.4% of his cases who had had diabetes for a period less than 5 years, and in 57.2% of his cases who had had diabetes for more than 5 years. In the study by Rabinowitch and his co-workers[1] of a large group of diabetics by various methods, previously mentioned it was found that of 162 individuals of 50 years of age and under who had had diabetes for 5 years or less, vascular disease was found in 64 cases, or an incidence of approximately 39%.

In the present study the findings appear particularly significant when one considers that the average age of the 22 diabetics recorded is 16 years and the average duration of the disease is slightly more than 3 years.

The results of the above studies justify the conclusions that arterial hardening appears prematurely in young diabetics. At the present time there is no definite evidence available to indicate why an increase of arterial hardening occurs prematurely in some diabetics and not in others. If this etiologic factor were known it would be of inestimable value in controlling and possibly eliminating the development of premature arterial aging in the diabetic, but until further evidence is forthcoming the idea must be accepted that every young diabetic is a potential arteriosclerotic. To combat the development of arteriosclerosis in diabetes several investigators (Joslin, Rabinowitch, Geyelin, Shepardson) have advocated the high carbohydrate and low-fat diet as opposed to the high-fat diet on the theory that diabetics who are on a high-fat diet develop a hypercholesterolemia, the presence of which may be an important factor in the production of vascular sclerosis. Whether the high-carbohydrate and low-fat diet will be effective in preventing arteriosclerosis or holding it in abeyance, however, remains to be ascertained by further studies. But regardless of what therapeutic measures are proposed to treat the diabetic it becomes apparent from this study that no treatment can be regarded as successful

unless it has become effective in checking the development of arteriosclerosis or the progression of the disease if it is already present. Only by accomplishing this can the diabetic's span of life be increased to approach that of the normal.

Summary. The pulse-wave velocity method was utilized in studying arterial elasticity in the large and medium-sized arteries of 22 young diabetics. To test the significance of the pulse-wave velocities obtained in this study the well known Chi-square test was employed. While the values for the transmission of the aortic pulse wave did not indicate any significant changes from the normal, those for the transmission of the radial pulse wave were definitely significant.

Conclusion. The diabetic state either initiates early or accelerates the development of premature arteriosclerosis in the young adult.

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7. Since the Chi-square test is only highly accurate when at least 10 cases are expected in each zone, it was applied to the zone above and the zone below the mean which are each expected to contain 10.5 cases. The differences remained significant since the probability was still only 1 in 1000. Boyd, E.: A Method of Establishing the Probable Limits of Normal Variation in the Weight of Organs, Anat. Rec., **62**, 1, 1935.

THE METABOLISM OF LEVULOSE.

VIII. THE INFLUENCE ON TOLERANCE OF CERTAIN NON-ENDOCRINE DISORDERS.

BY ALLAN WINTER ROWE, PH.D.,*

DIRECTOR OF RESEARCH, EVANS MEMORIAL HOSPITAL, BOSTON, MASS.,

MARY A. MCMANUS, A.B.,

GERTRUDE A. RILEY, A.B.,

AND

ALBERT J. PLUMMER, A.M.,

BOSTON, MASS.

(From Evans Memorial and Massachusetts Memorial Hospitals.)

IN a series of earlier papers certain aspects of the metabolism of levulose in humans have been reported, dealing severally with some general considerations,[1] the influences of hepatic dysfunction,[2]

* Deceased.

the levels of ovarian activity,[3] and the phases of the reproductive cycle.[4] Determinations have been made simultaneously of the effects of these various agencies on the utilization of pure galactose; these observations have served as controls, previous studies[5,6,7] having established criteria of usual performance. While both sugars are governed broadly by the general provisions of carbohydrate utilization, such as transformation to glycogen and ultimate oxidation to carbon dioxid and water, the earlier studies have clearly demonstrated that there are certain highly significant differences in the several mechanisms of the intermediate metabolism of these two sugars. The present paper deals with an extension of the earlier investigations to include a number of morbid states all unassociated with the endocrine system and all of which are generally recognized as influencing directly or indirectly the utilization of carbohydrates by the human body.

Method. In view of the more detailed statements of the previous papers, only brief reference need be made to the methods of study. Individuals presenting one of the conditions under investigation were hospitalized and thoroughly studied for a period of not less than 1 week. This served not only to document the presence of the primary condition with adequate objective evidence but also to evaluate the possible coëxistence of other secondary conditions which might independently influence the results of the study. This is of vital importance, particularly when the criterion of function level is no more than an end result susceptible to the influence of a wide variety of seemingly unrelated agencies. So far as possible, cases were selected which were demonstrably free from disturbing complications. In a few instances this general provision was abrogated to include some individual whose condition was of especial interest; all such cases will be noted in the body of the report.

Sugar tolerances were estimated by a modified Hofmeister[8] technique, for reasons previously discussed. Ten-gram gradations, as usual, were selected for the galactose test meals, while 25-gm. stadia were regarded as more appropriate for levulose with its significantly higher tolerance limits. The usual precautions as to adequate preliminary feeding for a period of days, basal state at time of testing with control of exercise and temperature, were rigorously observed.

Levulose was tested for qualitatively by the methods of Benedict and Seliwanoff, while the quantitative estimation involved a combination of the Benedict titration, Folin-Wu procedure after the use of Lloyd's reagent, the precision polariscope, and the use of controlled fermentations with washed yeast. The full analytical details are reserved for a later communication.

The composition of the study series together with a few descriptive details is presented in Table 1.

The present liver group is drawn only in small part from that earlier discussed,[2] cases with significant complication being largely excluded. Three of the series had histories of earlier neural damage

consisting severally of a fractured spine, hydrocephalus and a possible encephalitis; none of them gave current evidence of organic lesion at the time of examination. In addition, there was 1 case of treated syphilis with negative serologic tests but a positive gold curve in the spinal fluid. The hepatic status was defined by the summation of evidences derived from the history, physical examination, icteric index, van den Bergh, duodenal function (McClure), blood and urine studies, and the radiologic examination of the gallbladder (Graham).

TABLE 1.—COMPOSITION OF SERIES.

Subgroup.	Sex.			Age (yrs.).		
	Male.	Female.	Total.	High.	Low.	Average.
I. Hepatic dysfunction	10	30	40	71	13	34.2
II. Syphilis	6	10	16	66	5	34.6
III. Neural disorder	4	16	20	54	9	24.7
IV. Blood dyscrasia	8	4	12	73	20	53.7
V. Malignant neoplasm	8	2	10	65	15	49.5
VI. Infection	5	5	10	13	8	11.0
Total	41	67	108			

Five of the syphilitics were of congenital origin with characteristic physical stigmata supplementing the usual objective evidences. Practically all of the group had received extensive treatment but half of them still gave positive serologic response. One patient had an earlier history of head trauma but neurologic examination failed to disclose evidence of residua certainly attributable to it.

The group with neural disorders was highly diversified. One-half of the composing members had a traumatic background; there were 3 sisters with Friedreich's ataxia, single cases of diabetes insipidus, hydrocephalus, cord tumor, and postmeningitic and encephalitic conditions. All were carefully studied neurologically. Three were achondroplastic dwarfs.

The blood dyscrasias were also diversified, with 7 cases of primary anemia together with 2 of lymphatic (32,000 and 58,000 leukocytes) and 1 of myelogenous (1,236,000 leukocytes) leukemia, and 1 each of polycythemia (11,060,000 erythrocytes) and chlorosis. The anemias gave characteristic blood pictures, positive neurologic findings, and presented achlorhydria and negative response to neutral red. One diagnosis was further confirmed at autopsy. One of the lymphatic leukemia cases gave a positive duodenal function test indicating disturbance of biliary production, implying a degree of hepatic dysfunction.

The cases in the malignant group comprised 2 patients with Hodgkin's disease; the others all had neoplastic growths, primary in the stomach, prostate, larynx, pancreas and breast. Several had secondary metastases—in 2 instances to the liver—and 1 breast cancer was recurrent. One testicle case had been operated seemingly with success and, as will be shown later, had the only normal

galactose tolerance in the group. One of the throat cases had been earlier treated for lues; the current serologic tests were all negative.

The final group was composed chiefly of children with both badly infected tonsils and sinuses. An acute appendicitis presented in 3 of these and they were discharged for operation.

Except as indicated above, subversive complications were absent, and in a number of the positive reports significant current involvement could not be demonstrated.

The females are in ratio of 3 to 2 in the total group, a somewhat higher masculine proportion than that usually encountered. Exception is noted in the cancer and blood groups, in which also no children appear. The basis of the case selection renders the fact of no significance but prevents the sex factor, if any,* from playing a considerable rôle in the sugar study. The age scatter is a wide one in all but the last subgroup. The average ages reflect in some measure the primary conditions of the etiologic classification.

Blood and urine data are germane to the consideration of sugar metabolism even though glucose be the usual carbohydrate measured.

TABLE 2.—BLOOD AND URINE DATA.

Subgroup.	Urine, glycosuria + (%).	Blood sugar (mg.).		
		High.	Low.	Average.
Hepatic dysfunction	20	106	69	93
Syphilis	31	117	75	95
Neural disorder	10	107	78	90
Blood dyscrasia	8	118	84	94
Malignant neoplasm	20	113	85	96
Infection	0	...	..	..

Only the children of Group VI fail to show at least 1 case of glycosuria. One-fifth of the hepatic and one-third of the luetic groups present this evidence of disturbed carbohydrate metabolism, the figures comparing well (23% and 25%) with those deriving from much larger groups previously reported.[9] The other comparisons—malignancy 40%, blood dyscrasias 19%, and neural lesions 25%—show a less frequent incidence in the present series. So far as the metabolism of glucose may be equated with that of the other sugars this feature is desirable, as departures from the normal by the sugars under investigation gain an added significance. The blood sugars show nothing remarkable, both the range and average values falling within the conventional limits of the normal. Exception might possibly be made to the inferior limits in Groups II and III. These were single cases and the sole exceptions to an otherwise complete conventional normality.

Before discussing the sugar tolerances as actually observed, brief

* It seems very doubtful if there be a sex difference in the metabolism of levulose. See earlier citation.[3]

consideration must be given to the criteria of normal performance. These are collected in Table 3.

With the sex difference and the fluctuations in the levels for the female seemingly intrinsic in her degree of sexual maturity, data can be equated in a mixed series only by recording tolerances in terms relative to the normal standard for each individual. Galactose tolerances, for this reason, are reported as normal or as percentile deviations, indicating both direction and degree of departure from the norm.

TABLE 3.—NORMAL TOLERANCES.

Galactose (gm.).	Female.	Levulose (gm.).*
20	Prepuberal	75 to 100
20 to 40	Puberal	75 to 100
40	Adult	100 to 125
40 to 30	Postmenopausal	100 to 125
	Male.	
30	Child	75 to 100
30	Adult	100 to 125

* Values as given are approximate but conform to present data.[3]

Six of the liver group are at normal levels; the remainder exhibit varying degrees of depression. Further investigation of the 6 cases which conform to predicted tolerance shows that 4 of them are renal cases with definitely lowered renal permeability. The opinion has been expressed[10,11] that this condition retards the elimination of sugar and thus raises the apparent tolerance level; our own experience is broadly confirmatory to this postulate. The remaining 2 cases gave some evidence of renal involvement though not of sufficient magnitude to be considered in this connection. In addition, as one of us has shown elsewhere,[5] a small percentage of uncomplicated liver cases demonstrate an increased tolerance for galactose. This certainly implies that an occasional case could fall between the abnormal extremes and show a normal level.

TABLE 4.—GALACTOSE TOLERANCE.

	Deviation.					
			Below normal.			
Subgroup.	Above normal.	Normal.	±0 to −25.	−26 to −50.	Over −50.	Average (%).
Hepatic dysfunction	0	6	2	18	14	−46
Syphilis*	1	2	1	7	4	−37
Neural disorder†	0	2	1	10	5	−47
Blood dyscrasia	1	0	1	4	6	−46
Malignant neoplasm*	0	1	0	2	6	−54
Infection	0	3	0	5	2	−33
Total	2	14	5	46	37	

* One case not tested.
† Two cases not tested.

Syphilis shows a definite downward trend but not of marked degree. One case is above prediction, a man, aged 42, with cardiac disease but nothing in the diagnostic pattern to account for the anomaly. The 2 cases with normal tolerance were both nephritics.

A cardiorenal status offers possible explanation for 1 of the 2 neural cases with normal tolerance; the other was a child, aged 10, with a history of severe head trauma but with a negative neurologic examination.

The sole case in Group IV with abnormal response to galactose was a woman, aged 73, with primary anemia and a significantly impaired renal function. The normal cancer case has already been noted—a testicular tumor which had apparently been successfully operated and from which there were no demonstrated residua.

With the relatively slight influence exercised on carbohydrate metabolism by infective processes that do not acutely involve the liver, it is not surprising that several of the infection group show a normal tolerance.

Let it be noted, however, that with the exception of the few cases commented on above, the remainder of the series (85%) show a depression of galactose tolerance and in a measure best expressed by the report of the average deviation summarizing each subgroup.

Not only do these several states lower the utilization power of the organism for the customary sugar glucose, as shown by the appearance of glycosuria, but also the tolerance for galactose is significantly lowered in a very large number of the individuals presenting the several conditions under investigation.

The levulose data are collected in Table 5. Here the individual test-meal levels producing levulosuria are reported, as the normal standards are not as yet certainly defined. With the differences noted in the child and the adult, groups containing both are separated into their respective categories. This permits a tentative rough definition of normal, increased, or diminished tolerance on the basis of the standards given in Table 3. The data for the probable normals are given in heavy-faced type in Table 5:

TABLE 5.—LEVULOSE TOLERANCE.

Subgroup.	Positive test meal (gm.).						
	Over 150.	150.	125.	100.	75.	50.	25.
Hepatic dysfunction (a)	1	2	**3**	**5**	17	7	4
(c)	0	0	0	**0**	**1**	0	0
Syphilis (a)	2	1	**0**	**0**	7	2	0
(c)	0	0	0	**0**	**1**	1	2
Neural disorder (a)	1	0	**1**	**4**	3	3	2
(c)	0	0	0	**0**	**1**	2	3
Blood dyscrasia (a)	0	1	**1**	**5**	1	4	0
Malignant neoplasm (a)	2	1	**0**	**4**	2	0	1
Infection (c)	0	0	0	**4**	**4**	2	0
Total	6	5	5	22	37	21	12

Dealing with the data as they present and for the moment without reference to the equivalent galactose indications, it is evident that an appreciable number of cases with hepatic dysfunction demonstrate a normal utilization capacity. The trend with lues is unmistakably downward, but 3 of this small series report tolerances that are definitely increased. One-third of the neural group are normal or above, and over half of the patients with blood dyscrasias fall in the same categories. Malignancy produces but a very moderate depressing effect, the 3 cases below the normal being balanced by an equal number above normal prediction. Finally, only 2 of the children fall below the normal zone. While some depressing effect on levulose tolerance is manifested by each of the several conditions comprised within the study group, the influences are far less potent than in the equivalent response to galactose feeding.

This can be rendered more concrete by direct comparison. Reporting each case simply as normal, increased, or diminished, and waiving the possible greater nicety of arithmetical expression, a precision that is patently more apparent than real, the relative behavior of the two sugars can be contrasted.

TABLE 6.—COMPARISON OF DEVIATIONS.

	Deviations (%).					
	Above normal.		Normal.		Below normal.	
Subgroup.	Gal.	Lev.	Gal.	Lev.	Gal.	Lev.
Hepatic dysfunction	0	7	15	23	85	70
Syphilis	7	19	13	6	80	75
Neural disorder	0	5	11	30	89	65
Blood dyscrasia	8	8	0	50	92	42
Malignant neoplasm	0	30	11	40	89	30
Infection	0	0	30	80	70	20
Total	1.9	10.2	13.5	31.5	84.6	58.3

In the group of hepatic dysfunction there is a reasonable degree of correlation. Galactose utilization seems to be somewhat more uniformly depressed than that of levulose but both show the same general tendencies. This same observation applies to the luetic group, both sugars showing a lowered utilization in a majority of the cases.

In the neural group the agreement is distinctly less good. The galactose response is definitely more uniform than is that of levulose. In the blood dyscrasias there is an actual change in sign, with half of the levulose tolerances normal and only 42% depressed as against a 92% incidence of lowered tolerance in the galactose response. With the cancer group the discrepancy is even more marked, while in the last series 80% show a normal levulose and 70% a depressed galactose tolerance.

The differences in the intermediate metabolism of the two sugars, touched upon briefly in the opening paragraphs, here finds marked expression. In the last three subgroups and tendentially at least in the third, there is a lack of agreement in the behavior of the two sugars that is of wholly convincing proportions. Significant as are the divergencies here manifest, an even more rigid analysis can be made by comparing the results obtained with each sugar in the individual case.

TABLE 7.—CORRELATION.

Subgroup.	Agreement (%).
Hepatic dysfunction	68
Syphilis	80
Neural disorder	61
Blood dyscrasia	42
Malignant neoplasm	33
Infection	10

In spite of the relative concordance of the reports from the liver cases when they are assembled as a group, this present more-searching approach shows that but 2 in every 3 cases agree qualitatively, and this, let it be noted, waives the more rigorous comparison which would take cognizance of the relative quantitative relations. Correlation in the luetic series is high, confirming the indications of the previous comparison. The neural group shows a somewhat less satisfactory agreement than did the hepatic series, and the remaining three subgroups show a progressive lack of concordance that becomes almost complete in the children's series (Group VI). That this is not due to any influence intrinsic in childhood can be clearly demonstrated by a review of the results with children in the other groups.

TABLE 7a.—CORRELATION OF CHILDREN'S DATA.

Subgroup.	No. of cases.	Agree.	Disagree.
Hepatic dysfunction	1	0	1
Syphilis	4	3	1
Neural disorder	6	4	2
Total	11	7	4

In other words, the children, excluding those in Group VI, show an agreement of 64%, a value concordant with the averages of the several groups in which they occur. Patently one must seek further for the explanation of the discrepancies shown by the children with infections.

Discussion. A brief review of more recent literature discloses the wide array of contradictory reports which must inevitably occur where fundamentally different methods of approach and widely fluctuating criteria of positive response preclude a common basis for comparison. The general literature has already been briefly

reviewed in the first paper of this series.[1] A few citations germane to the text may be given here.

The influence of various types of hepatic disorders upon the tolerance for each of the sugars is still a field of active controversy with a steadily growing literature. A depressing influence of syphilis on levulose utilization has been reported,[12,13] and equally denied;[14] hepatic involvement was a feature in all of these series. Hurst[15] could find no abnormality of the blood-sugar curve with levulose in cases of paralysis agitans and cerebral vascular disease. The levulose response in primary anemia is reported as normal,[16,17] that to galactose as normal,[17] and to glucose as depressed.[18] Leukemia had no effect on levulose[12] and was depressed in but 1 case in 7 in a second report.[16] Polycythemia is reported both as a depressing influence[13] and as one without effect[16] on levulose tolerance. Malignant neoplasm does not depress the utilization of levulose[19] even when the liver was involved;[20,21] cancer of the head of the pancreas[22] gave positive response in 3 cases of 5 tested. Many of the citations given above report only a very small number of cases, in some instances only 1. The papers from the Mayo Clinic[14,16,22] form a body of valuable material, but the Tallerman[23] blood-sugar technique was used and this precludes a parity for comparison with the present studies.

To recapitulate briefly, in our own studies all of the conditions under investigation produce a downward trend in the power of the human organism to utilize galactose, a trend that assumes some magnitude in 85% of the cases. Fourteen patients show a normal tolerance with 2 more an increased tolerance. Of these, 6 are primary liver cases, possibly explicable on the basis of the sugar anomaly already noted.[5] One neural case and the testicular cancer gave no evidence of present disturbance. Four more were established nephritics and a lowered renal permeability may, but by no means certainly does, explain their failure to follow the characteristic trend. This leaves but 4 cases in the entire group whose observed tolerances depart from the expected level and for which no plausible explanation is now forthcoming.

Turning to the levulose reports on these 16 cases, 2 of the liver and 1 with neural damage are in agreement with a normal tolerance. To these should be added 1 luetic patient whose utilization capacity for both sugars is increased. Of the remainder, 4 hepatic, 1 luetic, 1 neural and 3 from the infection group show depressed tolerances, while 1 neural and 1 cancer patient are above prediction. The sole remaining case was the woman, aged 73, with primary anemia and an established nephritis who showed an increased galactose and normal (100 gm.) levulose tolerance. One-tenth of the total levulose reports are above and one-third more are normal. The relative concordance between the two sugars in the hepatic and luetic

groups, which constitute one-half of the entire series, tends to minimize in the series summation the marked deviations characterizing the other four categories.

That the liver plays an important but not identical rôle in the metabolism of the two sugars seems probable, although, as noted above, this is still a matter of active debate. If this assumption be correct, it might be postulated that lues mediated its influence through the liver and that this was the explanation of the relative —but far from complete—concordance in these two groups. Unfortunately for so simple an adjustment, the neural involvement in syphilis is not a matter of speculation, and in the neural group the trend is toward a lack of agreement in the response of the two sugars. This finds even more certain expression in that of the blood cases. Disharmony prevails in the cancer series in which 2 cases have demonstrated and a third a probable metastatic involvement of the liver. The 3 galactose reports on these patients are of a profound and uniform depression of tolerance; the levulose, on the other hand, shows a complete impartiality with 1 increased, 1 normal and 1 slightly depressed. Certainly the postulate that the liver is the sole agent mediating these abnormalities in carbohydrate metabolism cannot marshal any adequate array of supporting evidence. In like manner, the complete absence of hyperglycemia, particularly in the cases of long standing, rules out a hormonal pancreatic influence as the controlling factor.

Once again, the only inference which seems warrantable from this latest collection of mutually inharmonious data is that in the intermediate metabolism of these two sugars a variety of mechanisms are operative, some seemingly influenced qualitatively alike, at least, by agencies common to both, and others, as in the mammary effect,[3] in which only one participates. Further study with a wide variety of abnormal states of reasonably assured etiology may throw further light on the problem. For the present, nothing remains but to report the factual evidences derived by controlled experiment. In the material thus far secured may be found certain data which should help toward a final resolution of some of the contradictory reports so widely recorded in the literature.

Summary and Conclusion. In 6 groups of patients showing respectively hepatic dysfunction, syphilis, neural disorders, blood dyscrasias, malignant neoplasms, and infections, the tolerance to levulose was determined. The total series comprised 108 patients. The cases of 11 children showing hepatic dysfunction, syphilis and neural disorders are likewise reported.

The results, compared with those secured from the use of galactose as a test sugar, agreed in varying proportions from 10% in infections to 80% in syphilis. The discrepancies in the various groups are discussed.

It is concluded that in the intermediate metabolism of these two sugars a variety of mechanisms are operative, some seemingly influenced qualitatively alike, at least, by agencies common to both, and others in which only one participates.

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STUDIES ON TWO CASES OF URTICARIA FROM COLD SENSITIVITY AND OF THE EFFECT OF HISTAMIN TREATMENT.*

By Leslie L. Saylor, M.D.,
RESEARCH FELLOW, VASCULAR CLINIC,
AND
Irving S. Wright, M.D.,
CHIEF, VASCULAR CLINIC; ASSISTANT PROFESSOR OF CLINICAL MEDICINE, NEW YORK POST-GRADUATE MEDICAL SCHOOL AND HOSPITAL OF COLUMBIA UNIVERSITY, NEW YORK CITY.

(From the Vascular Clinic of the Department of Medicine, New York Post-Graduate Medical School and Hospital of Columbia University.)

The unusual dermatologic phenomenon of localized redness, burning and edema, following the exposure of the skin to cold and occurring with or without a generalized reaction has been reported by a number of investigators (mostly European) since it was first described by Béhier[1] in 1866. Horton and Brown,[2,3,4] Horton,[5] Duke[6,7] Blackford,[8] Bray,[9] Paul,[13] Dobbs,[11] Weiss[12] and Levine[13] have added reports of cases, with experimental observations, to the American literature since 1929. Levine has recently thoroughly reviewed the literature with a summary and discussion of the immunologic, humoral and neurovascular hypotheses of the etiology of the condition. He has included the report of 1 additional case.

Two cases of cold sensitivity are herein reported. Case 1 is more important: first, because of the unusually high temperature at which the reaction occurs, secondly, because it was possible to complete certain interesting experimental work, and, finally, because we were able to institute histamin therapy with definite improvement.

Case Reports. Case 1.—An unmarried lady, aged 32, who was born in Austria of Jewish parentage and who has been a resident of the United States for the past 15 years, came to this clinic on July 23, 1935. Her complaints, at that time, were localized itching and burning sensations as well as throbbing headaches and generalized flushing following the exposure of an area of her skin to cold air or cold objects. Following such exposure, an area of redness and wheal formation would appear at the site exposed. She also stated that she was unable to eat ice cream or chilled food because her throat would soon seem as though it were swollen, and she would have difficulty in swallowing. In May, 1934, she had an infection of the distal phalanx of the right index finger. She consulted a physician, and the finger was incised. Neither a local nor a general anesthetic was used. The finger drained, and healing was complete in 2 weeks. She did not receive any type of serum therapy. Approximately 2 months after the finger had healed, she noticed that, as she handled cold objects or washed her hands in cold water, this same finger became swollen and red. This phenomenon did not occur on any other part of her hands at that time. A few days later, however, the same reaction occurred on her hands, arms, feet and face. Her face would become extremely swollen when exposed to the cold winter air. The same would happen when she

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carried a cold milk bottle against the skin of her arms. Her condition was as above described on admission to the hospital. With the exception of the statement that she becomes nauseated and often vomits whenever she eats egg in any form, there is a negative personal and familial allergic history. Her past history revealed only the following significant facts. She has a history of but one previous illness: 15 years ago, while crossing the ocean, she developed a cough which was diagnosed as due to bronchitis. During the winter months, for 3 years, there was a recurrence of the same condition, as there was each time she went swimming during the summer. For the past 2 years, however, she has not had an attack, but, during that time, she has not been swimming. For the past 15 years she has had a feeling of swelling in her throat whenever she has eaten ice cream. Whether this reaction would have occurred before is open to question, since she never ate ice cream until her arrival in the United States. She continued to eat it until the summer of 1935, when it produced swollen lips to such a

FIG. 1.—Note swelling of left hand after exposure to cold water. Note also patch of urticaria on right arm, after application of ice locally.

degree that she discontinued frozen foods in all forms. The menstrual history is normal. There has been a gradual but not an abnormal increase in weight for 3 years previous to this last year, during which it has reached a plateau. Physical examination was negative as to anything abnormal except the reactivity of her skin to cold. Laboratory reports were as follows:

Blood count: red blood cells, 5,090,000; white blood cells, 9550; hemoglobin, 96%. Differential count: neutrophils, 72%; small lymphocytes, 19%; large lymphocytes, 6%; monocytes, 3%.

Urine analysis: clear; specific gravity, 1.018; sugar, negative; albumin, negative; acid reaction; microscopic examination: epithelial cells. No hematuria, hemoglobinuria or history of same.

Blood Wassermann: negative.

Experimental Studies. *Experiment 1.* The temperature at which the reaction would take place was determined by filling a small flask with

water and applying the flask to the forearm for a few minutes. The temperature of the water was gradually reduced, and, by recording the temperature of the flask as the temperature at which the reaction occurred, the results in Table 1 were obtained. Because the results obtained in this test seemed improbable, since the temperature of the object causing the reaction was unbelievably high, it was repeated (Experiment 1a). One would expect that this patient would be in a constant state of edema as soon as the room temperature reached 24° C. (75.4° F.). This, however, actually was not true. A modification of this test showed that the reaction depends entirely upon the actual temperature of the skin, which represents a resultant of the temperature of the object in contact with it, the heat conductivity of the object, and the generation of heat by the tissues beneath the point of contact. This was demonstrated as follows: the patient, while seated in a room of 22.3° C. temperature, for over an hour had no evidence of reaction. The skin temperature of her arm was 31.4° C. A metal cabinet, which had been a permanent fixture in the room, had a temperature of 23.5° C. or 1.2° C. higher than the room temperature. The cabinet, however, seemed cold, since it removed heat from the arm more rapidly than did the air; consequently, the arm became cooler, after it had been in contact with the metal for 4 minutes, and the skin temperature at the point of contact had been reduced to 27° C. A definite redness and edema appeared at the area thus cooled.

The temperature of an object applied to the skin was gradually reduced as in Experiment 1, to determine the skin temperature necessary for the production of the reaction (Table 1, Experiment 1a).

TABLE 1.—DETERMINATION OF TEMPERATURE AT WHICH REACTION OCCURS.

Experiment 1.

Room temp., ° C.	Temp. of material applied, ° C.	Time of contact, min.	Reaction.
25	26.4	4	Negative
25	25.4	4	Negative
25	24.0	4	Redness; distinct wheals

Experiment 1a.

		Temp. of skin with material applied, ° C.		
24	32.0	31.7	4	Negative
24	26.2	30.3	4	Negative
24	25.1	28.6	4	Redness; no edema
24	24.2	27.6	4	Redness; slight edema
24	24.0	26.8	4	Redness; definite edema

Control skin temperature of arm at room temperature: 31.4° C.

Experiment 2. The blood pressure, pulse and skin temperature and changes in size following the production of the edema in one hand and wrist are noted in Table 2, Experiment 2.

TABLE 2.

Experiment 2.

RESPONSE TO REACTION.

(Hand and wrist in 8° C. water—5 minutes).

Time.	B. P.	Pulse.	Circumference of wrist, cm.	Temperatures (° C.). Room.	Dorsum, hand.	Right cheek.	Left cheek.
Control . . .	140/86	102	15.75	24.6	32.5	35.8	35.1
Ten minutes after removal . . .	124/70	124	18.0	25.5	34.6	35.8	35.8

Experiment 3. The marked similarity of the patient's generalized response to induced cold urticaria and to histamin hydrochlorid injected subcutaneously is noted in Table 2, Experiment 2.

Experiment 3.

COMPARATIVE RESPONSE TO REACTION.

Histamin hydrochlorid 1 cc. (1 to 1000 sol.) subcutaneously.

Time.	B. P.	Pulse.	Cheek temp., ° C.
Control	146/90	92	34.2
5 minutes after histamin	132/68	135	
10 minutes after histamin	130/60	140	
15 minutes after histamin	126/76	126	36.1

Experiment 4. When a localized area of skin was exposed to cold, a very definite local vasodilation appeared, a prominent redness of the skin could be seen, and a marked increase in the skin temperature of this area resulted. This temperature rise was measured and noted in Table 3. Blood pressure and pulse readings are included.

TABLE 3.—TEMPERATURE (° C.) RESPONSE OF AREA EXPOSED.

Experiment 4.

	Room.	Dorsum, hand.	Mid-arm.	3d finger.	Left cheek.	Pulse.
Control	24.6	31.3	31.6	32.2	34.3	106
Hand and wrist in water 8° C for 5 minutes	..	..	..	..	..	112
10 minutes after exposure	24.6	35.7	34.1	33.6	36.1	

Control.	Hand in water 2 mins.	Hand in water 3 mins.	Hand in water 5 mins.	Hand removed 10 mins.
Blood pressure:				
142/90	146/94	130/88	122/84	138/94

Experiment 5. Bray[9] and Levine[13] were able to demonstrate, in their cases, local eosinophilia in a wheal produced by exposure of the skin to cold. This test was done twice on our case, but no eosinophilia appeared either time. The results are shown in Table 4, Experiment 5.

TABLE 4.—TEST OF LOCAL EOSINOPHIL RESPONSE TO COLD URTICARIA.

Experiment 5.

		I. Eosinophil count per 100 leukocytes.	II. Eosinophil count per 100 leukocytes.
Index finger before exposure		2	0
Same finger:	Whole hand in edema	0	0
	Half hour later	0	0
Opposite index finger:	Hand not exposed	0	0
	Half hour later	0	2

Experiment 6. Horton and Brown[3] showed the histamin-like effect of the production of cold urticaria on the gastric acidity. This test on our case confirms their findings (Table 5, Experiment 6).

TABLE 5.—HISTAMIN-LIKE EFFECT OF COLD URTICARIA ON GASTRIC ACIDITY.

Experiment 6.

Specimen.	Free acid.	Total acid.
Fasting	43	59

Remarks:

1. Hand in water 10° C. for 10 minutes. (Tourniquet at elbow.)
2. Tourniquet removed in 5 minutes.
3. Patient noted general effect, throbbing in head, 2½ minutes after removal of hand from water.

Specimen.	Free acid.	Total acid.
10 minutes after hand was removed	78	90
20 minutes after hand was removed	92	106

Experiment 7. The Perutz, Brugel, Greenfeld reaction, in which 10% menthol in alcohol is applied to an area of the skin, and which, when positive, either produces the same reaction as does the cold or causes the area to become more hypersensitive to cold, was negative in our case. An area of redness resulted, but there was no urticaria, and the area thus treated did not show an increased hypersensitivity to cold.

Experiment 8. Cold was applied to an area previously anesthetized with 2% novocain intracutaneously and subcutaneously. In our case, an area 5 by 8 cm., over the deltoid region, was anesthetized. All sensation to cold was removed. A test tube containing ice was applied for 5 minutes. Edema in the anesthetized area resulted, but it was not so marked as in the unanesthetized area.

Experiment 9. The Prausnitz-Küstner reaction: Venous blood was taken before and 25 minutes after exposure of the hand to ice water for 5 minutes; the second blood specimen was obtained 18 minutes after the edema appeared, at the time it seemed to have reached its maximum. The serums were separated and injected intradermally into a normal person. After it had been injected and the area cooled with ice for 5 minutes, neither serum specimen caused wheal formation. Levine[13] reported 6 positive and 5 negative results of other authors.

Experiment 10. By transferring some edema fluid from an area in which it had been produced by the application of ice to an area free from edema, Levine[13] produced a secondary urticarial wheal. Since he had used normal saline as a vehicle to infiltrate the edema and recover the edema-producing substance, he used a normal saline injection as a control, also. We repeated this experiment and obtained similar results by injecting 0.2 cc. of edema fluid within 3 minutes, an area of urticaria 2 by 2 cm. had appeared. When 0.2 cc. of normal saline was injected, no urticaria appeared.

Doctors Westcott and Spain, of the Allergy Clinic of this hospital, investigated by the use of 87 skin tests the possibilities of a sensitivity in this patient to inhalants and foods. They were, however, unable to discover any conclusive evidence of allergy, as indicated by skin testing.

Treatment. Because of the remarkable improvement in the case reported by Bray,[9] in which histamin hydrochlorid was used in the method of desensitization, we have instituted the same therapy. On August 5, 1935, only a few days after the patient's admission to our clinic, she received 0.1 cc. of 1 to 1000 histamin hydrochlorid intracutaneously. On alternate days she received another intracutaneous injection, each succeeding one having been increased by 0.1 cc. of the solution, until 0.5 cc. was given. Then 0.5 cc. was injected subcutaneously. This was increased by 0.1 cc. on alternate days, until 1 cc. was injected subcutaneously. This amount was tolerated physiologically but, because of the uncomfortable sensation of warmth and the marked throbbing headaches which resulted, it did not seem advisable to make further increase. The patient has, therefore, continued to receive 1 cc. of 1 to 1000 histamin hydrochlorid subcutaneously, 3 injections each week, and at the time of this report (December 16, 1935) has had 36 such injections. Objectively, the edema appears as rapidly as it did when she was first examined on July 23, 1935; at this time, however, the edema is not so severe and the time necessary for its subsidence is much less. Formerly, when her hand became edematous, when she placed it in ice water she was practically unable to move the fingers and the swelling would not subside until from 3 to 6 hours had elapsed; whereas, at this time, with the edema produced identically as before, even when it is at its maximum, she can move her fingers and almost completely close the hand. The edema entirely subsides in one hour. Symptomatically,

she no longer suffers the intense burning, the throbbing headaches and weakness that formerly accompanied the local reaction. At times, however, she still experiences mild burning accompanying the edema. Last winter she was unable to leave the house when the temperature was below freezing, whereas this year she has been able to go out in temperatures as low as 10° F. without marked symptoms. She believes that she is 60% improved.

We have not used calcium lactate as suggested by Dubbs[11] because we desired to determine the value of histamin alone. We intend to try it when and if the patient does not continue to improve under the present therapy.

CASE 2.—We are including, in addition, a report of a second patient whom we were unable to study in great detail but who also presents a definite clinical picture of cold sensitivity. This English woman, aged 40, is a very successful actress by occupation. She has since childhood been a strong swimmer and enjoyed especially the cold water of the British coast. In 1929, after plunging into cold water at Brighton, England, she collapsed, became unconscious and had to be taken from the water. She vomited and had a severe diarrhea. There was no generalized swelling, but innumerable "white lumps," up to 1 inch in size, appeared over her body. In 2 hours she had completely recovered, except for slight weakness. That evening she felt well but, the next day, on going into the water, the syndrome recurred. There had been no antecedent history of dietary indiscretion or any other possible exciting factors. She had no symptoms during the cold weather of the winter 1929–30, but, in the summer of 1930 when she tried swimming in cold water, the syndrome recurred. There was no further recurrence until the summer of 1934, even though she swam regularly in cold water. The symptoms returned in severe form when she tried to swim in cold water in 1934. During the winter of 1934–35, for the first time, the patient developed severe urticaria of any portion of the skin exposed to cold air. This was very disturbing, since she was often compelled to go to the theater an hour or more in advance of her performance in order that the disfigurement from the facial urticaria could subside. She also noticed that, if she took cold drinks or food such as ice cream, her lips would swell and occasionally this extended to the throat. The warm weather brought about a lessening of these symptoms but, in the summer of 1935, water less and less cold could produce collapse, unconsciousness, urticaria and the rest of the original syndrome. Finally, it was brought on when the water temperature was measured at 68° F. Physical examination revealed no significant findings. Application of ice to the surface of the forearm produced a pronounced wheal, approximately 1 square inch in area; at the same time the blood pressure of 130/75 dropped to 100/65. It is possible that this was the result of the production of "H" (histamin) substance. This test was repeated with similar results. Laboratory studies showed the following results:

Urine analysis: Clear; specific gravity, 1.016; acid reaction; no sugar or albumin; microscopic examination reveals epithelial cells.

Blood count: Red blood cells, 4,220,000; white blood cells, 4500; hemoglobin, 74%; polynuclears, 72%; small lymphocytes, 20%; large lymphocytes, 8%.

Blood-Wassermann: Negative.

Chemical examination of blood: Urea nitrogen, 14 mg.; sugar, 100 mg.; uric acid, 3.9 mg. Aside from a mild secondary anemia and a slight increase of uric acid, there were no findings of importance.

Unfortunately, it was impossible to study this patient in the detail outlined in our first case report, since she had to travel with her show.

Comment. Case 1 is of interest because the experimental studies seem to give more weight to the humoral hypothesis of etiology than to any other. The blood pressure, pulse, skin temperature and gastric acidity responses of the patient to the cold urticaria are very similar to those resulting when histamin is administered. We, therefore, deduce, in agreement with other authors, that these phenomena are due to an "H," histamin-like substance liberated from the tissue cells when they are exposed to certain degrees of cold. This substance is then taken up by the blood from the edematous wheal thus formed, which results in the production of the physiological responses which simulate those of histamin. Bray[9] states in his article, "It has been shown that histamin is liberated in the skin of normal people when the temperature of the skin is decreased to 20° F. (−6° C.)". In these cases of cold sensitivity, therefore, the threshold at which histamin is liberated is raised. In Bray's case, this threshold was raised 25° F. or from 20° F. to 45° F. Since the temperature of the skin of our patient, at which the reaction occurred, was 26.8° C. or 80.2° F., the threshold in our case is raised 60.2° F., an increase as compared with Bray's patient.

It is worthy of note that there was no evidence of allergy in Case 1 in the skin tests, in eosinophil counts, in the passive transfer of serum test (Prausnitz-Küstner reaction) or in a family and personal history. It is not clear, at present, why histamin, given as above outlined, has relieved this patient.

Case 2 is similar to cases reported by Graszl[14], Tannhäuser,[15] Lehner,[16] Netter,[17] zum Busch[18] and Affolter,[19] since this case first developed symptoms and became unconscious when swimming in cold water. This patient would probably have drowned had she not been rescued. It would seem, therefore, that wider dissemination of information regarding this syndrome should be undertaken. There are undoubtedly many unrecognized cases of this condition, and the dangers to these individuals, of swimming, tub-bathing or taking showers in cold water cannot be overemphasized. It is entirely possible that the reaction could be of such severity as to produce a depression of blood pressure that would be incompatible with life.

Summary. 1. Two cases of urticaria, both females, from cold sensitivity are reported.

2. In the first case rather extensive experimental studies were possible. The beneficial effects of histamin treatment were observed.

3. That the reaction occurred at an unusually high skin temperature in this case was demonstrated.

4. Experiment points towards the humoral hypothesis of cause of reaction.

5. The second case is reported primarily because of the complete collapse when swimming in cold water.

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ESSENTIAL HYPERTENSION.

II. Constitutional Considerations.

By Marcus Backer, M.D.,

Clinical Assistant in Medicine, Yale University School of Medicine, Bridgeport, Conn.

(From the Department of Internal Medicine, Yale University School of Medicine, and the New Haven Hospital and New Haven Dispensary.)

In the last few decades renewed efforts have been made to classify man into constitutional types and to associate certain disease-entities with one type of constitution or another. Much literature has accumulated on the subject, and a drastic divergence of opinion prevails among the various "schools" on many a cardinal topic. One has to proceed with great caution, therefore, in any study of human constitution in order to escape the temptation of biased and hasty conclusions.

With regard to essential hypertension, treatises on human constitution are conspicuous by their lack of an exhaustive independent

investigation of the matter. There are several textbook statements, however, as well as many publications in the current literature pertaining to this subject, which are at times very instructive, at others, confusing and contradictory. For instance, such an eminent pupil of DeGiovanni and Viola as Nicola Pende,[1] makes the observation that the habitus of cases of familial hypertension corresponds, among other things, to the hypergenital type. He adds that this accords well with the stimulatory action exerted upon the cardio-arterial tonus by the genital and other hormones. Yet, elsewhere in the same book, this distinguished author claims emphatically that the hypergenital or hypersthenic type of constitution is characterized by the absence of arterial hypertension. This contradiction, again, may be contrasted with the opinion of such authorities on human constitution as Julius Bauer[2] and Ludwig Braun[30] who find no characteristic habitus of any kind in cases of essential hypertension. Recently, Zipperlen[3] examined a series of cases of essential hypertension, and found an overwhelming prevalence of the hypersthenic, pyknic, or apoplectic type of constitution. Barr[39] of St. Louis, discussing Cushing's still very debatable[40] hypothesis of pituitary basophilism in relation to hypertensive disease, expresses the opinion of many observers that the numbers of basophilic cells in the posterior pituitary lobe are greater in hypersthenic than in asthenic individuals, "thus in general tending to show predilection for the type of patient statistically most likely to have high blood pressure." Conversely, Fossier[4] and several others[5, 6, 8] depict the asthenic "tall and slender, longnecked . . . , usually emaciate" individual with the "elongated flattened chest of the paralytic type" and with the "weakness of the abdominal parietes" as the bearer of the directly opposite picture, namely, essential hypotension.[42] Similarly, a somewhat dimensional terminology[19] describes a "linear type" with low blood pressure, and a "lateral type" with high blood pressure.

Etiologically, Fossier's conception of the narrowing of the aortic arch in hyposthenic subjects offers a purely mechanical explanation of "essential" hypotension; fetal "toxic infections," in such individuals, with endocrine (adrenal) damage and consequently[5] lowered vascular tonus form the basis of another pathogenetic hypothesis; finally, in contradistinction to the hypertensive subjects, these "hypotensive[18] weaklings" are exposed as cases of constitutional mesenchymatous inferiority with a weakness of the muscular[13] and supportive tissues, exemplified by their enteroptosis, drooping shoulders, poor musculature, prominent scapulæ, and flat feet. Whether or not one subscribes to this last or to any other etiological belief, at any rate one observes, for a while, some degree of harmony between the two anthropological findings: the pyknic,[31] apoplectic, lateral, or hypersthenic[10] individual with essential hypertension on one hand, and the asthenic, or better, hyposthenic, with essential

hypotension, on the other. This balance of views, however, is soon gravely disturbed, when such an outstanding student of blood pressure as Kylin[7] reports cases of habitus asthenicus some of whom show a high, some others a low blood pressure. Kylin then proceeds to conclude that hypotension and hypertension are not at all syndromes of diametrically opposite nature but that they represent, instead, different phases of one and the same disorder—a conclusion which, despite Kylin's authority, should be regarded with considerable mental reservation.[18] The question is rendered even more difficult by some other observations of the occurrence of essential hypotension[8] in the hypersthenic type and of essential hypertension[9] in asthenic and other types[33] of bodily habitus. An altogether speculative note of discord is sounded in some quarters in the form of an assertion that the constitutional factor in essential hypertension is to be conceived "not in terms of physical but of mental[16] properties."

"With the idea[12] of a constitutionally increased neuromuscular tonus of the arterial system as the starting point in the study of essential hypertension," as presented in our previous publication, one might be tempted to emerge from and to abandon this swift current of gross morphologic anthropometric views because they are so divergent and because, above all, they may appear to be clinically and even theoretically entirely irrelevant. However, such an attitude may be quite erroneous. In the first place, from a general standpoint, the constitutional habitus is never an isolated coincidental phenomenon, but merely one aspect of a given constitution characterized[11] by a certain composition of the blood-plasma, certain chemical processes in the tissues, certain immunological reactions,[13] certain qualities of the endocrine apparatus and of the vegetative[14] system, and, clinically, stigmatized by the presence or absence of a predisposition to certain internal diseases.[20] In the second place, from a cardiovascular point of view, not only deviations from the normal tonus of the circulatory apparatus, especially the level[13] of arterial[23] tension, but also many another[11] inadequacy[23] of the heart[17] and bloodvessels are characteristically related to certain types of constitutional habitus. In this connection, one can hardly escape the thought of a possible relationship between the predominance of the asthenic habitus among the Chinese[17] and the strikingly low incidence of hypertension[21] among the same. If such views are correct, then, other things being equal, the blood pressure level of an individual may furnish a means of evaluation of the somatic constitution of that individual.[15] And, *vice versa*, barring cases of nephritis, adrenal neoplasms, etc., one may be able to estimate approximately the level of arterial tension under average circumstances from the examination of the physical constitution of the given person, alone.

Faced with these problems, the objective student of essential

hypertension will do well to remain keenly interested in their final solution. If a relationship between bodily habitus and blood pressure were now clearly established, both factors, the habitus as well as its corresponding arterial tension, would most likely have to be traced to a much deeper underlying *common cause* possibly appearing early in the course of ontogenetic events. The real nature of that intrinsic cause as well as of its resultant constitutional effects would have to be understood: Are we dealing with a purely morphologic problem of *mesenchymatous* origin with one aspect in the structural elements of the arterial wall and many another manifestation in the structures responsible for the bodily habitus, *i. e.*, the architectural constitution of the whole organism? Or is it perhaps entirely a problem of "the vegetative[12] neuromuscular tonus" alone, in the arteriolar as well as in any other tissues involved, regardless of their histological origin or kinship? If the latter be the case, are these constitutional differences of tissue function actually primary, and do they solely depend upon the given autonomous[29] nervous system, or is the arterial tonus for example, "only secondarily under the influence of vagal[24] impulses" because the autonomous nervous system is ultimately "under the control of the endocrine[24] glands?"[30] (Pituitary[34] and midbrain.[36] "Pituitary basophilism," Cushing.[32] Adrenals.[35])

Long before one can answer any of the above questions it is first imperative to find whether or not there actually exists *any* common constitutional denominator for the arteriolar tissues concerned with the maintenance of arterial tension and any other tissues of pertinent significance. The writer deems it consistent with the assumption of "a constitutionally increased neuromuscular tonus[12] of the arterial system" in cases of essential hypertension first to determine whether or not such a constitutional common denominator may be found in this very phenomenon of *tissue-tonus*, a phenomenon which Yandell Henderson[22] has justly labeled "one of the most fundamental properties of life."

Deeming it wise, therefore, to refrain at present from adding statistical data on the debatable prevalence of a certain habitus in cases of essential hypertension, I propose, instead, to investigate the possible existence, to begin with, of a constitutional factor of tonus in general, and its relation to arterial tension in particular. The following is, of course, merely one approach to this question, and not a final analysis.

Assuming that essential hypertension is merely one of many clinical manifestations of a hypertonic type of constitution, then the incidence of essential hypertension in hypotonic persons, *i. e.*, in those with a diminished neuromuscular tonus, should be correspondingly low. In order to ascertain this, the blood pressure has been studied in a group of cases all of which presented a hernia acquired some time in life without injury to the site of the hernia. Such spontaneously acquired hernias are to be regarded as positive

evidence of the fact that the tensile strength of the connective tissues involved is lowered, and that the tonus of the local muscular structures is also diminished. Such[37] hernias show a very marked hereditary predisposition,[38] when repaired with utmost surgical dexterity still strongly tend to recur, and such hernias together with enteroptosis, asthenic chest-configuration, and other related findings are viewed by Tandler, J. Bauer, K. H. Bauer, and others, as signs of a hypotonic constitution. K. H. Bauer, in dealing with this constitutional type remarks, in passing, that "hypertension and arteriosclerosis in the asthenic are practically unknown."[28] Conversely, hernias of all types are rare if present at all in the pyknic or hypersthenic subject.[41]

It need not appear objectionable to attempt to study comparatively the blood pressure, *i. e.*, the expression of the arteriolar *smooth* muscle tonus, and the nature of the tonus of "*voluntary*" muscular elements such as we are concerned with in cases of hernia. This somewhat antiquated arbitrary division line between exclusively autonomous and exclusively "animal" innervation as applied, respectively, to smooth and striated muscle fibers, is now no longer[42] an accepted dogma.[25] One need only mention the consensus of authoritative opinion expressed recently at an International Neurological Congress.[26] The second part of the program of that Congress was devoted entirely to the subject of muscle-tonus; a threefold tonic innervation of voluntary musculature was presented, namely, cerebrospinal, sympathetic, and parasympathetic; special emphasis was laid on the sympathetic influence upon the musculature, and experimental proof was offered of the existence and course of sympathetic nerves in the motor muscle fiber.

The possible finding of a low incidence of essential hypertension in cases of spontaneously acquired hernias might not be surprising to those who believe that the entire picture of a hypotonic constitution is the end-result of a generalized "mesenchymatous[28] constitutional inferiority" with an insufficiency of all the supportive tissue including the smooth and skeletal musculature, and cardiovascular, especially arterial, hypoplasia. Furthermore, by way of contrast, such findings would be in harmony with the demonstration by Kernohan *et al.*, of the Mayo Clinic,[27] of arteriolar hypertrophy in cases of arterial hypertension. One may wonder, as these authors do, if the morphological picture of the arterial wall might not be the *primary* underlying factor.

Irrespective of what may be the answer to this question, we wish to find at this time whether or not the arterial neuromuscular tonus of an individual is a factor coëxistent with a similar neuromuscular tonus in this individual in tissues other than the arteries.

This investigation comprises a group of 148 cases of spontaneously acquired hernias—the majority from the New Haven Hospital and New Haven Dispensary; some are private patients of the writer. After ascertaining beyond reasonable doubt the non-traumatic

nature of the hernia in each instance, 21 cases were excluded from this study; some because of a coincidence of a disease which tends to lower the blood pressure, such as chronic tuberculosis, others because of the presence of a factor tending to raise the blood pressure, such as plumbism or nephritis. The latter was responsible for the elimination of only 2 cases, 1 a patient of 25 without any arterial hypertension, another a person of 32 with a blood pressure of 150/95. Three cases of cryptorchism on the side of the hernia (inguinal) were excluded because of a possible congenital factor in the development of the hernia. Finally, no blood pressure readings were used when taken after sedative medication had been administered to the patient.

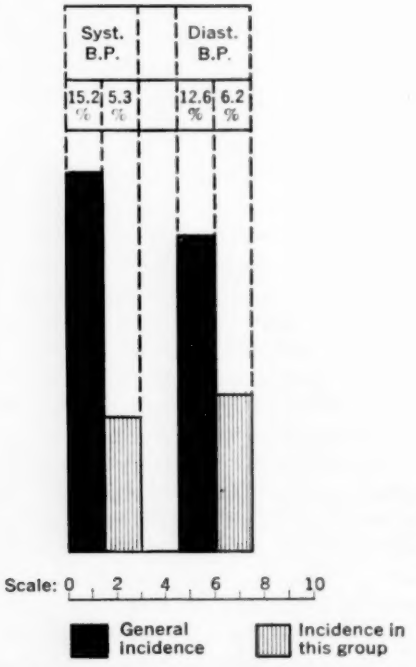

FIG. 1.—The general incidence of high blood pressure and its incidence in cases of spontaneously acquired hernias: males, all ages.

Since the incidence of hypertension in this group is being compared with the general incidence of hypertension as reported by Gager[44] in his large group of consecutive patients, the writer adopted Gager's criteria of normal blood pressure, namely, a systolic pressure of 140 before the age of 40, 150 after the age of 40, and a diastolic pressure of 90. After the elimination of the above referred to 21 cases, the remaining 127 patients were divided into 113 males and 14 females. The males only were analyzed in individual age groups conforming to the analysis of Gager. Except for the small female

group and the old age group of 60 years and over, the findings in all other cases are presented in graphic form in the accompanying three figures showing side by side the comparison of the incidence of high blood pressure in Gager's group of consecutive cases and in this group.

Fig. 1 compares the collective findings in males of all ages. It reveals a 5.3% incidence of systolic hypertension in our entire male

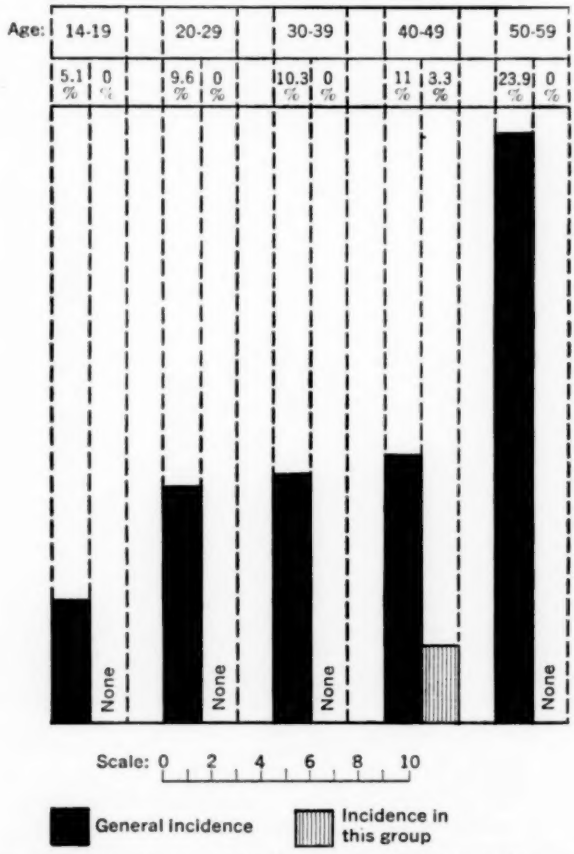

FIG. 2.—The general incidence of high blood pressure and its incidence in cases of spontaneously acquired hernias: systolic blood pressure, males.

group as compared with an expected incidence of 15.2% and a 6.2% incidence of diastolic hypertension as compared with an expected incidence of 12.6%.

Fig. 2 compares the findings of systolic hypertension in 5 individual groups of males analyzed according to age. The incidence of systolic hypertension in this series of cases in all given age groups except one is *nil* as compared with the corresponding figures of the

expected incidence of systolic[45] hypertension. The age group 40 to 49 alone shows the occurrence of some systolic hypertension, namely, 3.3% as compared with an expected incidence of 11%.

Fig. 3 shows the comparative data of the incidence of diastolic hypertension according to age. In 3 out of the 5 age groups the incidence of diastolic hypertension in our cases is *nil* as compared with the corresponding figures of the expected incidence in the same age groups. The age group 30 to 39 shows a 5% incidence of dias-

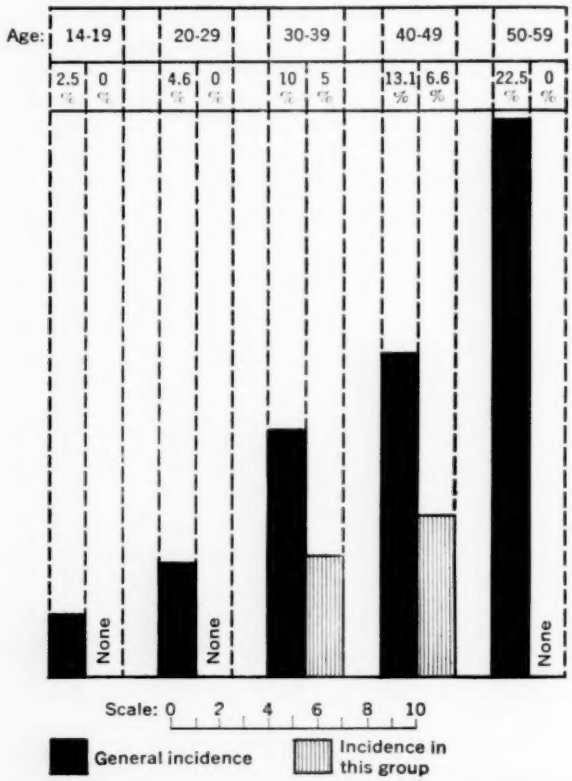

FIG. 3.—The general incidence of high blood pressure and its incidence in cases of spontaneously acquired hernias: diastolic blood pressure, males.

tolic hypertension in our cases as compared with an expected incidence of 10%. The age group 40 to 49 shows a 6.6% incidence of diastolic hypertension in our cases as compared with an expected incidence of 13.1%.

The comparative findings in the male patients of 60 and upward for which no tabular illustration is provided are as follows: In the age group 60 to 69 the incidence of systolic hypertension is 27.7% as compared with an expected incidence of 48.7%.

For the diastolic hypertension, an incidence of 16.6% in our male cases of 60 to 69 years stands out against an expected incidence of 33.7%.

In the last group of our male patients, of 70 years and over, there is an incidence of 16.6% systolic hypertension as compared with an expected incidence of 33.3%. This age group, however, is exceptional with regard to its incidence of diastolic hypertension. It is the only instance of a higher incidence in our cases than the expected incidence, the former being 16.6% and the latter 11.1%.

In our 14 female patients ranging from the age of 28 to 71 there was no instance of systolic hypertension and but 1 instance of diastolic hypertension. The latter occurred in a woman aged 71 years.

It is perhaps of some pertinent interest to note that the hernias of 35 of the patients investigated in this study were strikingly multiple, and that 4 patients had repeated recurrences some time after competent hernioplasty had been performed. These facts should not be unexpected in these individuals if their supportive tissues are constitutionally inadequate, and if they should prove to be stigmatized by a low neuromuscular tonus.

Be that as it may, the above referred to findings can be reasonably summarized in the statement that in this group of cases of spontaneously acquired hernias, the incidence of hypertension was disappearingly small as compared with the expected incidence of hypertension.

Conclusions. The number of cases studied in this investigation is limited. So is the object of this paper limited. It aims at an approach to the problem of primary hypertension from a constitutional point of view. It does not pretend to establish any new truths but to point the way in the direction of their possible existence. The writer hopes to arouse sufficient interest in this method of approach to the problem of hypertensive disease to induce others to undertake similar investigations. These should not, of course, be restricted to the finding of a strikingly low incidence of hypertension in subjects of a generalized low tissue tonus such as manifested by spontaneously acquired hernias. The possibility of a common constitutional background behind the tonus of the arteriolar musculature and the tonus of other supportive tissues in the same organism should be investigated in more than one way. The ultimate goal of such investigations is not merely to find the hereditary nature of essential hypertension or its possible prevalence in any one type of bodily habitus or in any type of constitutionally stigmatized individuals. The chief purpose of such investigations is much rather to find whether or not essential hypertension together with any other established coëxistent pertinent findings are all explicable on the basis of a certain genetically predetermined type of constitution. The specific question is: Does the strength of the original mesodermal foundation of an individual manifest itself in due time, and of inevitable necessity, in a certain strength of

tonus of the mesenchymatous derivatives including the smooth arteriolar musculature? If this be so, the generally blamed but, so far, unclarified immediately responsible blemish of increased peripheral resistance in the arteriolar bed of essentially hypertensive patients shall eventually be understood and its significance irrevocably linked with the sealed somatic fate of its bearer.

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45. Palmer, R. S.: Ibid., **94**, 694, 1930.

BOOK REVIEWS AND NOTICES.

INFECTIONS OF THE URINARY TRACT. By T. E. HAMMOND, F.R.C.S., Surgeon, The Royal Infirmary, Cardiff; Consulting Urologist, The Welsh National Memorial Association. Pp. 250; 3 illustrations and 3 charts. London: H. K. Lewis & Co., Ltd., 1935. Price, 10/6.

THIS book is valuable not only to persons interested in urology but also should be of interest to the general practitioner. It takes up in a systematic way not only the infections of the urinary tract but also discusses inflammations in general. The infections of the urinary tract are discussed in an orderly fashion and include those due to colon bacillus, Staphylococcus albus and aureus and to the gonococcus. There is some mention of tuberculosis of the urinary tract but the author does not take this up to any great extent. The urinary antiseptics used are about the same as those known to us and there is some mention of ketogenic diets. The author's conception of urinary tract infections in general seems to coincide very well with our own ideas of these conditions. The book is appended with interesting discussions of (1) the bearing of the constitution upon bacterial disease, (2) some points in the nursing of bacterial disease, and (3) the practice of medicine—all of which are interesting and helpful.

F. E.

ROENTGENOGRAPHIC TECHNIQUE. By DARMON ARTELLE RHINEHART, A.M., M.D., F.A.C.R., Professor of Roentgenology and Applied Anatomy, School of Medicine, University of Arkansas; Roentgenologist to St. Vincent's Infirmary, Baptist State Hospital, Missouri Pacific Hospital and the Arkansas Children's Hospital, Little Rock, Arkansas. Pp. 431; 183 illustrations. Second Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1936. Price, $5.50.

TIME has already established the usefulness of this textbook. While the general plan of the book is similar to the first edition, its value is enhanced by the edition of many recent advances in radiology. The first 12 of its 21 chapters contain discussions of Roentgen ray machines, the nature and properties of Roentgen rays, dark room technique, exposure combinations and various other physical factors concerned with applied radiologic physics. The rest of the book describes most of the roentgen examinations used by radiologists today. The verbal descriptions are excellently illustrated by photographs of patients in position for examination with roentgenograms obtained of each technique.

E. P.

THE HARVEY LECTURES, SERIES XXX. By DOCTORS WILLIAM BOSWORTH CASTLE, WILLIAM CUMMING ROSE, WILBUR A. SAWYER, ALFRED N. RICHARDS, E. C. DODDS, G. V. ANREP, FRANCIS G. BLAKE, and JOHN H. NORTHROP. Delivered under the Auspices of the Harvey Society of New York, 1934–1935. Under the Patronage of the New York Academy of Medicine. Pp. 270; illustrated. Baltimore: The Williams & Wilkins Company, 1936. Price, $4.00.

THE latest volume of this well known series presents 8 lectures, all by well known authorities in their special fields. The wide range that is covered is readily shown by the list of lectures and their subjects: "The Etiology of

Pernicious and Related Macrocytic Anemias," by William B. Castle, of Harvard; "The Significance of the Amino Acids in Nutrition," by William C. Rose, University of Illinois; "The Present Geographic Distribution of Yellow Fever and its Significance," by Wilbur A. Sawyer, The Rockefeller Foundation; "Processes of Urine Formation in the Amphibian Kidney," by A. N. Richards, University of Pennsylvania; "Specificity in Relation to Hormone and Other Biological Reactions," by E. C. Dodds, The Middlesex Hospital, London; "The Relation of the Circulation in Voluntary and Plain Muscle to Activity," by G. V. Anrep, Egyptian University; "Pneumothorax in the Treatment of Pneumonia," by Francis G. Blake, Yale University; "The Isolation and Properties of Crystalline Pepsin and Trypsin," by John H. Northrop, The Rockefeller Institute. Adverse criticism does not occur to the Reviewer and praise seems superfluous. E. K.

ABORTION. Spontaneous and Induced. Medical and Social Aspects. (This volume is one of a series dealing with medical aspects of human fertility sponsored by The National Committee on Maternal Health, Inc.) By FREDERICK J. TAUSSIG, M.D., F.A.C.S., Professor of Clinical Obstetrics and Clinical Gynecology, Washington University School of Medicine, St. Louis. Pp. 536; 146 illustrations, and 27 tables. St. Louis: The C. V. Mosby Company, 1936. Price, $7.50.

THE extreme importance of abortion as a medical and social problem of the present time justifies the appearance of this very comprehensive monograph upon the subject. The conservative figures offered for the United States refer to 681,600 abortions annually, with a death toll of 8179. These data are believed to be minimal. The socio-medical aspects may be briefly summarized in the known fact that one of every four puerperal deaths follows an abortion.

A wide review of the world's literature for years back is utilized to form a historical and factual background upon which the author has developed his picture of the present day situation, with its clinical, pathologic, legal and social aspects.

Of interest from a standpoint of comparative obstetrics is the chapter by Dr. W. L. Williams of Cornell University on abortion in animals. Suggestive, at least, is the discussion of trichomonas as a possible cause of abortion in animals.

The chapter on prevention details the various measures which may be used either before or during pregnancy or to prevent uterine contractions. Taussig is skeptical as to the value of hormone therapy in prevention. Very important is the chapter on treatment, displaying a frankly conservative attitude toward febrile abortions.

The indications for therapeutic abortion, a chapter twice as long as any other in the book, carries one widely afield as the author reviews the reasons found in the literature for the interruption of pregnancy. In the discussion he follows Winter's outline. The relation of sterilization to this procedure is discussed. The attitude of Russia toward legalized abortion is discussed in a separate chapter, although the reaction of other European countries is interestingly mentioned here. Although misquotation of portions of this chapter occurred in a recent lay journal review of this book, one feels in reading the closing sections of this chapter that the author is quite broad-minded toward a widening of the socio-economic indications for therapeutic abortion.

The legal and medico-legal aspects of abortion are fully considered. The laws of the states and countries are annotated and the medico-legal aspects of abortion provide words of wisdom and caution for the practitioner.

This most able presentation of one of our most serious and common problems deserves to be widely read, and the book belongs on the work shelf of every obstetrician. P. W.

NEW BOOKS.

Disinfection and Sterilization. By ERNEST C. MCCULLOCH, M.A., D.V.M., PH.D., Biological Research, Pennsylvania Salt Manufacturing Company, etc. Pp. 525; 53 illustrations, 232 tables. Philadelphia: Lea & Febiger, 1936. Price, $5.50.

The Patient and the Weather. Vol. 1, Part 2, Autonomic Integration. By WILLIAM F. PETERSEN, M.D., with the assistance of MARGARET E. MILLIKEN, S.M. Pp. 781, lithographed; 366 illustrations. Ann Arbor: Edwards B others, Inc., 1936. Price, $9.00.

Frigidity in Women. Its Characteristics and Treatment. By DR. EDWARD HITSCHMANN and DR. EDMUND BERGLER, Director and Assistant Director, respectively, of the Psychoanalytic Clinic in Vienna. Authorized translation by POLLY LEEDS WEIL, of New York. Pp. 76. Washington: Nervous and Mental Disease Publishing Company, 1936. Price, $2.00.

Marconiterapia. Trattato sulle Onde Corte. Nella Biologia e nelle Applicazioni Terapeutiche. By PROF. PIETRO CIGNOLINI, Capo del Reparto Radiologico ed Aiuto volontario dell'Istituto di Clinica Medica Generale della R. Universita di Genova. In collaboration with PROF. F. BARATTA, ING. A. ASCIONE and DOTT. C. BIANCHI. Preface by PROF. GIUSEPPE SABATINI, Direttore della Clinica Medica Generale della R. Universita di Genova. Pp. 362; 152 illustrations and 12 tables. Milan: Ulrico Hoepli, 1936. Price, Lire, 50.

Security Against Sickness. A Study of Health Insurance. By I. S. FALK. Pp. 423. Garden City, N. Y.: Doubleday, Doran & Co., Inc., 1936. Price, $4.00.

Die Tuberkulose. No. 5 of Volume 16 (May, 1936). Sonderheft zur Deutschen Tuberkulosetagung in Warnemünde. By Various Contributors. Pp. 30. München: Otto Gmelin, 1936. Price, M. 2.40.

Principles and Practice of Recreational Therapy for the Mentally Ill. By JOHN EISELE DAVIS, B.A., M.A., Senior Physical Director, Veterans Administration Facility, Perry Point, Md.; Fellow of The American Physical Education Association, in collaboration with DR. WILLIAM RUSH DUNTON, JR., Instructor in Psychiatry, The Johns Hopkins University. Pp. 206. New York: A. S. Barnes & Co., 1936. Price, $3.00.

Die "Atypische" Pneumonie. Eine klinisch-röntgenologische und differential-diagnostische Studie, zugleich ein Beitrag zur Frage der "Grippe" und des Frühinfiltrats. (Special Vol. 6 der Sammlung Immunität, Allergie und Infektionskrankheiten.) By DR. MED. FRANK KELLNER, Facharzt für Lungenkrankheiten, leitender Arzt der Tuberkulose-fürsorgestelle Kassel. Pp. 52; 10 illustrations. München: Otto Gmelin, 1936. Price, Paper, M. 2.70; Bound, M. 3.60.

Methods of Tissue Culture in Vitro. By RALPH BUCHSBAUM, PH.D., Department of Zoölogy, University of Chicago, and Outlines of Histological Methods, with Special Reference to Tissue Culture, by CLAYTON G. LOOSLI, PH.D., Department of Anatomy, University of Chicago. Pp. 81, lithographed; 19 illustrations. Chicago: The University of Chicago Press, 1936. Price, $1.00.

Aktive Entspannungsbehandlung. Ein Neues Therapeutisches Prinzip mit Berücksichtigung der Sprache und Atmung. By DR. MED. JOH. FAUST, Hannover. Pp. 112; 20 illustrations and 2 plates. Leipzig: Hippokrates-Verlag G.M.B.H., 1936. Price, Paper, Rm. 5; Bound, Rm. 6.20.

Operative and Interpretative Radiodontia. A Textbook for Students and Practitioners of Dentistry. By WALTER S. THOMPSON, D.D.S., Associate Professor of Radiodontia, College of Dentistry, University of Southern California; Lieutenant, U. S. N. R., Special Service Instructor in Radiodontia, etc. Pp. 374; 355 illustrations. Philadelphia: Lea & Febiger, 1936. Price, $7.00.

Medizinisch-chemische Bestimmungsmethoden, Vol. 2. Eine Auswahl von Methoden für das klinische Untersuchungslaboratorium. By DR. KARL HINSBERG, a. o. Professor Vorsteher der Chemischen Abteilung des Pathologischen Instituts der Universität Berlin. Pp. 186; 48 illustrations, many tables. Berlin: Julius Springer, 1936. Price, Rm. 8.70.

Amino Acid and Ammonia Metabolism in Liver Diseases. By ESBEN KIRK. Pp. 147. Copenhagen: Levin & Munksgaard, 1936. Price, Dan. Kr. 10.

On the Disturbance of the Circulation in Spinal Anæsthesia. An Experimental Study. Suppl. 43 of Vol. 78 of Acta Chirurgica Scandinavica. By OSCAR O. SCHUBERTH. Pp. 77; 2 illustrations and 30 tables. Stockholm: P. A. Norstedt & Söner, 1936. (No price given.)

Synopsis of Diseases of the Heart and Arteries. By GEORGE R. HERRMANN, M.D., PH.D., Professor of Clinical Medicine, University of Texas, etc. Pp. 344; 88 illustrations and 3 color plates. St. Louis: The C. V. Mosby Company, 1936. Price, $4.00.

Psychiatry for Practitioners. Vol. 7 of the Oxford Medicine. By Various Authors. Edited by HENRY A. CHRISTIAN, A.M., M.D., LL.D., SC.D. (HON.), Hersey Professor of the Theory and Practice of Physics, Harvard University; Physician-in-Chief to the Peter Bent Brigham Hospital, Boston. Pp. 634, with 12 of Supplementary Index. New York: Oxford University Press, 1936. Price, $10.00.

Pathological Physiology and Clinical Description of the Anemias. yB WILLIAM BOSWORTH CASTLE, M.D., S.M. (HON.), Associate Professor of Medicine, Harvard University; Associate Director, Thorndike Memorial Laboratory and Junior Visiting Physician, Boston City Hospital, and GEORGE RICHARD MINOT, M.D., S.D. (HON.), F.R.C.P., EDIN. (HON.), Nobel Laureate in Medicine, 1934; Professor of Medicine, Harvard University; Director, Thorndike Memorial Laboratory and Visiting Physician, Boston City Hospital. Edited by HENRY A. CHRISTIAN, A.M., M.D., LL.D., SC.D. (HON.), Hersey Professor of the Theory and Practice of Physic, Harvard University; Physician-in-Chief, Peter Bent Brigham Hospital, Boston. Pp. 205. New York: Oxford University Press, 1936. Price, $3.00.

Johannes de Mirfeld of St. Bartholomew's, Smithfield. His Life and Works. By SIR PERCIVAL HORTON-SMITH HARTLEY, C.V.O., M.A., M.D., F.R.C.P., Consulting Physician to St. Bartholomew's Hospital, and to the Brompton Hospital, etc., and HAROLD RICHARD ALDRIDGE, M.A., formerly Scholar of Peterhouse, Cambridge, etc. Pp. 191. Cambridge: At the University Press. New York: The Macmillan Company, 1936. Price, $4.50.

Treatment in General Practice. The Management of Some Major Medical Disorders. 1. Articles Republished from the British Medical Journal. Pp. 250. New York: Paul B. Hoeber, Inc., 1936. Price, $3.50.

L'Esthétique Mammaire à Travers l'Histoire. By DR. CLAOUÉ and I. BERNARD. Pp. 24; 8 illustrations. Paris: Librairie Maloine, S. A., 1936. (No price given.)

NEW EDITIONS.

Exophthalmic Goiter and Its Medical Treatment. By ISRAEL BRAM, Medical Director, Bram Institute for the Treatment of Goiter and Other Diseases of the Ductless Glands, Upland, Pa., etc. Foreword by R. G. HOSKINS, PH.D., M.D., Director of Research, Memorial Foundation for Neuro-Endocrine Research, Harvard Medical School, Boston. Second edition, completely revised and enlarged. Pp. 456; 79 illustrations. St. Louis: The C. V. Mosby Company, 1936. Price, $6.00.

Ameisensäure als Heilmittel. Kurzer Leitfaden für ihre Anwendung. By SAN.-RAT DR. MED. ALBRECHT REUTER, Greiz. Second edition. Pp. 14. München: Otto Gmelin, 1936. Price, M. 0.68.

PROGRESS
OF
MEDICAL SCIENCE

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF
OSKAR KLOTZ, M.D., C.M.,
PROFESSOR OF PATHOLOGY, UNIVERSITY OF TORONTO, TORONTO, CANADA,
AND
W. L. HOLMAN, M.D., C.M.,
PROFESSOR OF BACTERIOLOGY, UNIVERSITY OF TORONTO, TORONTO, CANADA.

RECENT WORK ON THE TISSUE CHANGES IN VITAMIN "A" DEFICIENCY.

MANY reports have been published on the tissue changes which are found in animals that have been fed diets deficient in vitamin A. Only a comparatively small number of the more recent and more important papers will be discussed in this review.

Since 1922, when McCollum and his associates[1] separated the two vitamins in cod liver oil, vitamin A has been known to be essential for growth in young animals, and many investigators have even assigned to it a special growth promoting effect. For example, Sampson, Dennison and Korenchevsky,[2] in a series of painstaking experiments, showed that young rats deprived of vitamin A excreted somewhat more N, and grew much less per gram of food eaten than did litter mates fed the same amount of the corresponding adequate diet. The experiments were terminated when the avitaminotic rats showed the sudden drop in food consumption which usually precedes the last week of life. In other words, they showed that the metabolic rate was increased to some extent in vitamin A deficiency. Braman and his collaborators[3] obtained the same general results in similar experiments, although in this case all the rats were first depleted of vitamin A before they were fed the complete or the nearly vitamin A free diet. The differences in weight gain were less marked under these conditions than in Sampson's experiments. Recently Chevallier and Baert,[4] studying the metabolic rates in normal and vitamin A deficient rats, found that in the latter it was increased about 13%. However, this increase would not be sufficient to explain more than a small part of the decreased body weight.

Orr and Richards[5] have recently challenged the statement that vita-

min A is preëminently growth-promoting. They admit, of course, that as an essential food factor it has an effect on growth. These workers demonstrated definite growth in length of the leg bones during the period when the rat was losing weight on an A free diet, and suggest that the loss in weight is due to pathological changes, especially in the gastro-intestinal system. Even after 3 or 4 weeks on the diet, such lesions were seen in 75% of the animals and they suggest that microscopic lesions might be present a week or so earlier, at the time when the weight curves of the deficient animals begin to fall below those of the controls. That earlier lesions are likely is supported by Mouriquand's experiments,[6] where, by means of a special light and a corneal microscope, he demonstrated ulceration of the cornea in animals that had been fed the A deficient diet for only 18 days—fully 3 weeks before the development of gross xerophthalmia. At the present time the question of a specific growth promoting effect of vitamin A is not settled.

The effect of the lack of this factor on the endocrine organs has also not yet been solved. In their classical experiments, Wolbach and Howe[7] (1925) stated that the pancreas, thymus, thyroid, pituitary and testes showed atrophy as compared with the glands of adequately fed controls. The parathyroids and adrenals showed no decided decrease in size. All the rats were fed only 5 gm. a day, which is less than they would ordinarily consume. Korenchevsky[8] was unable to confirm these findings when he compared the organ weights per 200 gm. of body weight in A deficient rats, and in controls fed the same amounts of a complete diet. The testes in the deficient animals were heavier, but histologically they showed edema and degeneration. The prostates and seminal vesicles were also heavier in the A deficient animals. No change in percentage weight was noted in the adrenals, thyroid, hypophysis and thymus. De Ruyter[9] has recently stated that the thyroid shows atrophy in severe vitamin A deficiency, and that there is also involution of the thymus. Vitamin A therapy corrected these changes. The changes in the thymus may be connected with the decreased rate of growth. Coplan and Sampson[10] have recently studied the effect of a deficiency of vitamin A on the thyroid gland of rats. In the males they found the thyroids consistently smaller in the avitaminotic rats than in the controls. The converse held true for the females, although these all died within 37 days. On section, they found early a hyperplasia of the epithelial cells, which became high and dome shaped and looked similar to those seen in rats fed iodin deficient diets. Later the epithelium degenerated and this seemed to be specifically caused by a lack of vitamin A. They suggest that the A deficiency at first alters the metabolism of the thyroid epithelial cells, so that iodin is not normally absorbed or utilized and this causes a relative deficiency of iodin with the consequent thyroid hyperplasia. Lockwood and Hartman[11] found the adrenals atrophied in vitamin A deficient rats as compared with normal controls when calculated as per cent of body weight. Blumenfeld[12] also found atrophy of the adrenals, chiefly of the cortex, unless marked infections were present when hypertrophy supervened. Vogt[13] found that the pituitary of healthy men up to 50 years contained a constant quantity of vitamin A. After 60 years the vitamin content was less, and the slow growth of tumors in such individuals may be due to this cause. The

relation of vitamin A to the growth hormone was not solved. Nothing as yet suggests that overfunction of the thyroid explains the increased basal metabolism. Mason and Wolfe[14] were unable to demonstrate any definite abnormality in the endocrine activity of the ovary or pituitary in vitamin A deficiency.

Metaplasia of Epithelial Tissue. Wolbach and Howe,[7] in their excellent experiments which were reported in 1925, demonstrated that striking structural changes occurred in the epithelia of the nose and upper respiratory tract, the ducts and acini of the salivary glands and pancreas, the ureters, pelvis of the kidney, the bladder, many of the genital organs, the cornea and the paraocular glands of rats fed diets lacking vitamins A and D. The epithelium of the seminiferous tubules and the kidney tubules did not show this metaplasia. According to Mendel,[15] metaplasia of the trachea and bronchi is not common and usually only atrophy of the lining cells is found. In general, it has been regularly found that various types of epithelium, of entodermal, mesodermal or ectodermal origin showed the same morphologic changes. Atrophy of the cytoplasm of the original epithelial cells, which may be so slight as to necessitate comparison with normal cells to show it up, always preceded the later changes and possibly stimulated them. Then small nests of deeper staining epithelial cells appeared at intervals in the basal layer. These grew in all directions either as clumps or sheets and spread out underneath the original epithelium which retained its viability until it was entirely undermined. The old epithelium was sloughed off and the new squamous epithelial cells multiplied rapidly and in the upper layers showed keratinization. Some later workers found that the metaplasia varied from isolated nests to complete transformation. It has also been suggested that the decreased secretion of the associated glands promotes desquamative changes. Ducts of glands, small bronchi, or ureters may be blocked by the keratinized cells that are being formed and sloughed off with the resultant formation of cysts or abscesses. Wolbach and Howe[7] found considerably fewer epithelial infections in their rats than did Goldblatt and Benischek[16] or Green and Mellanby.[17] The infections are usually caused by bacteria which normally are present at the sites involved, and their development is favored by the poor drainage, the dead tissue and the lack of ciliary action and mucus secretion which are the sequels of the metaplasia. Goldblatt and Benischek confirmed Wolbach's work and showed that similar changes were caused by a diet deficient only in vitamin A. Seifried[18] studied the tissue changes in the chicken in great detail and found them to be essentially the same as those in the rat.

It is thought that the blood supply of the skin epithelium is poor,[19] which would probably mean a low concentration there of vitamin A, and the absence of this vitamin has been found to stimulate cell multiplication (*i. e.*, in new growths).[20] This may explain the constant normal growth of the epidermis. When vitamin A is deficient in the diet, all the epithelial tissues would be low in this factor, and this lack, following the stimulation of the original atrophy of the normal epithelium, may give rise to the multiplication and later keratinization of the squamous cells. This typical transformation of epithelial cells in many localities of the body, commonly known as metaplasia, has been found to occur in many different species of animals when vitamin A

free diets are fed. For example, human beings,[21] monkeys,[22] mice,[23] rats,[7] guinea pigs,[24] chickens,[18] rabbits,[22b] all respond in this way. Swine[25] and cows[26] also show similar gross pathologic changes. In a great many cases only a few of the many possible sites show metaplasia, and in a group of animals of the same species, age, sex and litter considerable variation is commonly seen in the order and number of the organs involved and in the extent of the metaplasia.

In a good many experiments only the gross lesions, such as abscesses, have been recorded. Whether or not an abscess occurred would probably depend to some extent on the type of bacteria which happened to be present at the site of the metaplasia. Chance variations in the number and variety of the bacteria may explain some of the variations found. Also it is possible that the vitamin A storage due to previous feeding varies and that animals vary in their ability to absorb and utilize this vitamin. Considerable variations are also found when we compare the results of vitamin A free diets in various species of animals. For example, the mouse does not show metaplastic changes in the salivary gland at the base of the tongue, whereas cysts or abscesses at this site are very common in the rat; the pig does not develop xerophthalmia, whereas the rat frequently does so.

Lesions in the Nervous System. As early as 1914 Hart and McCollum[27a] noted that pigs kept on diets of wheat and salt mixtures developed striking incoördination which could be cured if butter was fed. These same workers 2 years later[27b] fed pigs a diet largely whole wheat and containing little vitamin A, and found that after about 9 months the animals developed incoördination of the muscles and even blindness. Sections of the spinal cord showed shrunken motor nerve cells, apparently compressed by fluid about them. The processes were partly degenerated, the nuclei shrunken and the Nissl granules crowded together. The addition of either meat scraps or alfalfa, *i. e.*, mainly protein, or vitamin A, with some mineral salts as well, prevented the onset of the disease, which was thought to be due to the toxicity of the whole wheat. The same symptoms also occurred in dogs.[28]

In 1926 Mellanby[29] noted that dogs fed a diet deficient in the fat soluble vitamins and rich in cereals developed symptoms attributable to nerve lesions. Degenerated nerve tracts in the spinal cord were demonstrated in these animals. Since 1929 several investigations on this question have been carried out.

Hughes and his collaborators[25] found that pigs fed vitamin A deficient diets did not develop xerophthalmia, although some had watering of the eyes and slight swelling of the eyelids. They regularly after 6 months or more showed incoördination, spasms and blindness, apparently of nervous origin. Hearing and smell seemed also to be impaired. By the Marchi method they found definite annular degeneration of nerve fibers in the optic thalamus, optic, femoral and sciatic nerves, and in certain parts of the spinal cord. These nervous symptoms could be prevented or cured by adding various sources of vitamin A to the diet.

E. Mellanby has investigated this problem extensively, and has published a series of papers.[30] His diets contain large amounts of cereals and no vitamin A. The nervous manifestations were not invariably produced unless some apparently toxic substance such as wheat germ or ergot was added as well. The addition of vitamin A would prevent

the symptoms and also cure them promptly if they were of short duration. Lesions of long standing were, however, beyond repair. Young dogs, rabbits and rats were used. The symptoms included incoordination, paralysis, abnormal head movements and probably deafness.

Degenerative changes were found in the myelin sheaths of the nerve fibers in the spinal cord, and there was more degeneration in the cervical than in the lumbar region. The anterior columns (which contain sensory tracts in the dog), the anterolateral, the lateral posterior column (Burdach's) and the direct cerebellar tracts were commonly involved. In other words, the sensory columns seemed to be particularly picked out. The degeneration was seen in fibers scattered about in the tracts and not in groups of fibers lying together. The crossed pyramidal tracts were usually, but not always, free from degeneration and a few descending tracts which were associated with the midbrain or medulla suffered. The changes were not accompanied by cell invasion or other evidence of inflammatory reaction. If the nervous symptoms were allowed to continue for some time the fibers ultimately disappeared.

The peripheral nerves also showed degeneration. Although not entirely confined to afferent peripheral nerves, these showed the more intense degenerative changes (demyelination) and this applied both to the afferent spinal nerves and to other sensory nerves (optic, vestibular and cochlear of VIII, and sensory division of trigeminal).

In a rabbit showing early xerophthalmia, a few degenerated fibers were found in the first division of the trigeminal which supplies sensory fibers to the surface of the cornea. In more severe xerophthalmia, more advanced nerve lesions were found. If xerophthalmia was present in one eye but not in the other, sometimes some degeneration was found in the nerve supplying the normal cornea and sometimes it was not. Mellanby suggests that possibly the nerve and epithelial changes arise synchronously and that the generalized epithelial metaplasia is the result of the involvement of the afferent nerves throughout the body. In the early stages the myelin droplets did not invade the axis cylinders, but appeared as rings when stained with osmic acid. The whole nerve fibers were swollen. In more advanced cases many fibers were found in which degenerated myelin occupied the positions of the original axis cylinders. The degenerative changes affected only the first two neurones of the afferent nerves.

The motor cranial nerves escaped, although occasionally some degeneration was found in the third. If the nutritional disturbance had been very prolonged, some of the anterior nerve roots showed degeneration. As yet no degeneration has been found in the vagus nerve, even in its afferent fibers.

Degenerative changes were also seen in the nerve cells, including those of the dorsal roots, the Gasserian ganglion, Clarke's column, the Purkinje cells and the vestibular nucleus. It is seen here also that it is the afferent side that suffers most, although in the midbrain, the red and the oculomotor nucleus, and the dentate nucleus in the cerebellum sometimes suffer some changes.

M. Mellanby[31] demonstrated marked thickening and irregular downgrowths of the epithelium about the gingival margins, widening of the sulci and frequent pyorrheal infections in dogs fed vitamin A free

diets. Recently M. Mellanby and King[32] have demonstrated degenerative changes in the fibers of the sensory nerves which supply these sites, and also in nerve cells in the Gasserian ganglion.

It is quite possible that the primary lesions are in the nerve cells and that the fiber changes are secondary. The changes in the nerve cells are unfortunately very variable. The Nissl granules may appear powdery, may be clumped around the nucleus or the periphery or may be absent. The nucleus may be swollen, shrunken, eccentrically placed or absent. Even in the animals fed the adequate diet a few of the nerve cells are abnormal, but Mellanby assures us that the changes in the animals fed the diet deficient in vitamin A are much more marked and widespread. As yet there is no suggestion why the sensory nerve cells are injured and the motor nerve cells largely spared. Also, are we to suppose that the primary atrophy of the original epithelium which Wolbach and Howe emphasize, and also the initiation of the squamous differentiation of the basal cells are due to changes in the trophic nerves? It is possible that the squamous cells of the normal skin are poorly supplied with nerve fibers, and this type of differentiation may follow when there is a lack of nerve impulses to restrain the multiplication of the epithelial cells, such as might occur in areas innervated by such partially degenerated nerves.

Zimmerman[33] and Aberle[34] observed similar clinical signs in rats fed a vitamin A free diet containing cornstarch, but no cereals. They found myelin degeneration in the sensory tracts on the periphery of the cord in all their animals, but the posterior columns were involved in only about one-half of them. The medullary sheaths of the brachial plexuses and sciatic nerves always showed degeneration, but in addition 4 of 8 animals examined showed degeneration of the vagus. As a result of their staining methods, they concluded that the changes in the peripheral nerves were of longer duration than those in the cord. They occasionally found changes in the motor tracts and the anterior roots. They suggested that lesions in the cord followed those in the peripheral nerves on the sensory side and produced those in the peripheral nerves on the motor side. Animals which were fed the deficient diet for 5 weeks, but which showed no nervous signs, had normal nerves, but one rat which showed no clinical symptoms after 58 days on the diet had extensive peripheral myelin degeneration. The authors suggest that possibly it would have developed symptoms soon. Animals which were killed 4 days after they had been cured of their nerve symptoms by 20 days' treatment with cod liver oil, still showed moderate degeneration of the peripheral nerves and pyramidal tract. Possibly if a longer interval had elapsed between the cure and the examination more improvement would have been seen in the nerves. These authors also demonstrated that partial starvation but with adequate rations of vitamins did not cause lesions of this nature.

Sutton, Setterfield and Kraus[35] introduced two new methods into the study. Their rats were fed the A deficient diet until they stopped increasing in weight (60% showed incipient ophthalmia) and were then given about 30 mg. of butter daily. If no vitamin A (butter) was given they became so weak and emaciated that the nerve changes could not be properly observed. After about 2 weeks on this low A diet they showed incoördination of their back legs, and gradually they became

unable to use them. These authors found the Marchi process unsatisfactory and used instead a method in which the nerves were cut in frozen sections and examined with a polarizing microscope. Normal myelin consists mostly of cerebrosids, phosphatids and sulphatids which rotate the plane of polarized light (anisotropic) and is almost entirely free from true fats. When myelin degenerates it changes from a mixture of these substances to true fats (triglycerids) which do not rotate the polarized light (isotropic). Prior to the onset of ophthalmia, swelling of the axis cylinders and nerve fibers and some irregularity of the myelin was seen. Later, vesicular areas of isotropic degeneration appeared in the myelin. The number of fibers involved increased with the length of time the animals were kept on the partially deficient diet. If the animals were fed the same diet with supplements of carotene from weaning, the nerves showed no changes. These authors also suggest that the early degenerative changes in the nerves may be responsible for the epithelial metaplasia. The animals at no time showed spasms or convulsions, possibly because their diet contained no cereals. Some other authors claim that the accuracy of this method for showing myelin degeneration has not been established.

Seifried[36] made a study of the nerve lesions occurring in hens fed vitamin A free diets. Clinically the birds showed ataxia, incoördination, drowsiness and convulsions. The changes in the spinal cord fibers resembled those found by the other investigators, but in addition the anterior horn cells showed definite degenerative changes. Degenerative changes in the myelin sheaths in the sciatic, brachial and optic nerves were observed. In the brain a variety of very definite pathologic changes as observed in the ganglion cells of the motor cortex, of the nucleus dentatus, of the nuclei of the medulla oblongata, and more seldom in the Purkinje cells of the cerebellum. In other words, more changes were found in the motor nerve cells by Seifried than by the other investigators.

John[37] found the sensibility of the cornea in advanced stages of vitamin A deficiency in man to be markedly reduced, whereas conjunctival sensibility was much less reduced. He believes these findings are evidence of a central nervous system lesion. Bloch also stated that children suffering from xerophthalmia were very indolent in the first stages and later extremely irritable.

Suzman and his collaborators[38] tried without success to produce nerve lesions in adult dogs by feeding a diet devoid of vitamin A. These authors suggest that their dogs died of some other unknown deficiency before the nervous signs of vitamin A deficiency developed.

Grinker and Kandel[39] found that 4 monkeys fed an A deficient diet of poor quality (polished rice and aërated butter) showed neither nervous symptoms nor degenerative lesions postmortem. It was not stated whether the monkeys were adults. Weil[39] reported that 8 young rats fed on a synthetic A free diet did not show any marked weakness of their hind legs or any changes in their nervous systems. Davison[39] also was unable to confirm Mellanby's findings in rats fed similar diets. Neither of the last two authors have reported their findings in detail.

Hale[40] described in 1933 3 litters of pigs farrowed by sows on a vitamin A deficient ration which were without eyes or blind.

Night Blindness. Mellanby[41] found that the retina of a rabbit fed a diet deficient in vitamin A for 4 months was much thinner than that of the control rabbit. In the bipolar and ganglion layers particularly there were fewer cells which stained less intensely. The nuclei were eccentric and the Nissl granules powdery in the ganglion cells. In a dog that had been fed a similar diet for over 7 years the whole ganglion cell layer in the retina had disappeared and the optic nerve had been replaced by connective-tissue strands.

Wald[42a] has recently demonstrated by spectrographic methods that vitamin A is present in the retina, pigment epithelia and choroid layers of frogs, pigs, sheep and cattle. This same worker[42b] has also shown that the retinas of frogs that have been kept in darkness for 16 hours (dark adapted) contain visual purple but only a trace of vitamin A. Visual purple when treated with chloroform yields a new carotenoid, retinene, which is probably combined with a colloidal protein to form visual purple. Light-adapted frog retinas on the other hand contain vitamin A but no retinene. In an eye in which the retina and inner layers are intact, visual purple is regenerated from vitamin A. Some vitamin A is lost in the cycle and for normal vision must be made good from the diet. Vitamin A, according to this author, is "a simple though special component" in the visual purple cycle.

Skin. Very few investigators have described changes in the skin and epidermal structures of animals fed vitamin A free rations. Steenbock and his collaborators,[43] however, in 1922 found that in rats, especially if they were over 4 months of age, the hair became thin and bushy, growths appeared on the skin of the ears, tail and nose, and eventually sores developed on the body and legs which healed with difficulty. Possibly these growths on the ears and tail were due to mites as these are prone to occur in such animals.[44] None of these changes would appear to be specifically caused by a deficiency of this vitamin. Manville[45] found that such animals showed decreased activity of the sebaceous glands, with dry bristling hair that readily fell out. Gudjónsson[46] noted also that the fur lost its smoothness and that the feet became scaly and rough. Klemola[47] has described a keratoplastic reaction in hoof formation in the horse, also due to a lack of vitamin A.

In 1883 De Gouvêa[48] stated that keratomalacia was associated with a dry, scurfy-looking skin which was less sensitive than normal and that the hair fell out. Such findings have frequently been reported since.[49a] For example, Bloch[49b] observed that infants suffering from this eye condition had dry, scaly, shrivelled skins. Occasionally bleaching of the hair has been noted also.[50]

In their report of an autopsy on a 5-months-old infant that died with keratomalacia, Wilson and Du Bois[51] noted that the skin had a peculiar waxy feel and that there was slight desquamation on the abdomen.

Recently, Pillat[52] and Frazier and Hu[53] have reported two series of cases of keratomalacia associated usually with skin changes. The patients were adult Chinese and the skin lesions usually preceded those in the eyes. Both authors noted that the skin was dry and covered either with fine branny or larger scales of horny epithelium. In some cases the skin was darker than normal and took on a dull slate color. There were many comedones on the face and the hair was dry and lusterless. None of the patients showed signs of scurvy, beri-beri or pellagra.

The diet included white cabbage and salted vegetables and the former would provide enough vitamin C to rule out the possibility of scurvy. Pillat's patients suffered from multiple painless skin infections which cleared up rapidly with a high vitamin A diet. Frazier and Hu noted that the skin appeared finely wrinkled in places. The most striking finding in these patients was an eruption of usually raised papules (spinous, according to these authors) at the sites of the hair follicles on the extensor surfaces of the upper and lower limbs, the lower abdomen, the chest and the buttocks. The papules were usually deeply pigmented. Microscopically, they found that the epidermis around the papules was moderately hypertrophied, although later authors have described it as markedly hypertrophied. The mouth of the follicle was plugged by a dense mass of cornified material, laid down in more or less concentric laminæ—which one would expect was the product of metaplastic cells lining the follicle. The plugs either projected beyond the surface of the skin or were flush with it. The lower part of the follicle was atrophied and sometimes cystic and there was an increase in the intracellular pigment in the surrounding epidermal cells. Considerable numbers of lymphocytes, fibroblasts and occasional endothelial cells were found in the reticular tissue around the follicle. Only a few remnants of sebaceous glands were seen in the midst of the inflammatory zone. The ducts of the sweat glands were dilated and occluded by keratinized material, and the epithelial cells of the tubules were shrunken and irregular. The lumen of the glands was dilated. Pustulation occurred in about one-third of the cases. The infection apparently started in the plugs and spread into the perifollicular tissue. Ulcers were sometimes seen in the lining tissues of the distended follicles. No local treatment was used, but after 2 weeks of a high vitamin A diet the skin was definitely moister. The ulcerative lesions healed promptly. The papules decreased in size slowly and finally disappeared, leaving delicate atrophic pigmented scars. The cases were followed at the most for only 2 months and the skin had not become normal within that time. These findings fit in so perfectly with those seen elsewhere in vitamin A deficiency that it is hard not to believe them specific. Wiltshire,[54] however, described very similar lesions in cases of latent and manifest scurvy amongst Serbian troops.

In 1933 Loewenthal[55] described an almost similar condition among East African prisoners. The papular eruption was present in all cases of xerophthalmia and night blindness. It occurred chiefly on the extensor surface of the arms and outer and front surfaces of the thighs. This author noted that the dryness of the skin did not include that of the face or scalp. Itching was common. He gave 1 ounce of cod liver oil daily, leaving the rest of the diet unchanged, and no local treatment was applied. All of the night blindness and xerophthalmia and 98.6% of the dermal lesions were cured after 9 weeks of this treatment.

Nicholls of Ceylon[56] reported the same general findings and called the condition phrynoderma (toad skin), after the native name. Two-thirds of the patients who were suffering from this affliction had eye symptoms such as dimness of eyesight. Keratomalacia was only found in one-eighth of these patients. In the later stages they frequently developed neuritis and diarrhea and some deaths resulted.

Goodwin[57] has recently reported a case with a similar eruption in a 10-year-old child in England. It was associated with a smooth red tongue and apparently pyorrhea. On a high vitamin A diet plus 4 drachms of cod liver oil daily, the dryness of the skin, the eruption, and the yellowness of the conjunctiva disappeared, the tongue papillæ regenerated and the gums improved in from 3 to 6 weeks.

Sweet and K'Ang[58] from China have recently described 16 cases of keratomalacia. Only some of them showed the typical papules described above and the incidence was therefore considerably lower than in the other series, but most of these patients were very young.

Nicholls[59] also described a condition of "sore mouth" in which the patient showed patches of superficial erosion in the mucous membrane of the lower lip or tongue and later a red glazed tongue. It was only about one-quarter as common as phrynoderma. About 80% of the sore mouth patients showed phrynoderma as well. Glazed tongues have been described in rats fed diets deficient in the vitamin B complex. In deficiency diseases in man, usually several food factors are lacking and the resulting pathologic picture is very complicated. Nicholls stated that the Cingalese diet was very short in fat soluble vitamins and probably also in vitamin B_2.

MacKay[60] has reported some interesting results with English infants, half of whom were fed milk and solid food, and the other half the same diet plus extra vitamin A (a concentrate made from mammalian livers). The latter group showed a considerably lower incidence of skin infections, such as sore buttocks, intertrigo, and dribbling rashes. No obvious change in skin texture preceded this. No alteration was noted in general resistance or growth.

Several authors have found skin infections of various kinds furunculosis, pyodermia, ulcers[49, 61] and so forth, usually common among individuals suffering from vitamin A deficiency. For example, Spence[62] found that two-thirds of his 17 patients with night blindness and xerophthalmia suffered from persistent skin infections which cleared up rapidly, as did also the eye symptoms, when an adequate diet including cod liver oil was fed. Bloch[63] found severe infections, including pyodermia, common in his xerophthalmic children. For further references to such cases see MacKay's excellent review.[64]

Stomach and Intestines. In their early work (1925) Wolbach and Howe[7] stated that no metaplastic changes were found in the stomachs and small or large intestines of vitamin A deficient rats. Later (1933)[65] these authors found that the forestomach of such rats, which is normally covered with squamous epithelium, shows focal hyperkeratosis. Several other investigators, including Fujimaki, Fridericia, and Moll and his collaborators,[66] have reported similar findings. Fujimaki stated that the hyperkeratosis and papillomata were more marked if the diet contained considerable fat. When exclusive fat diets, even containing considerable amounts of cod liver oil, were fed, similar changes were observed. However, such a diet is so deficient in many other food factors that the results are of questionable value. Fridericia examined by laparotomy the stomachs of a series of rats that had been fed a vitamin A free diet intermittently for 18 weeks. They showed papillomata. They were then fed a normal diet for a year. At the end of that time the papillomata had disappeared in 19 of the 21 rats. The

epithelial overgrowths seem therefore to be definitely due to this specific deficiency. Moll *et al.* found the flat epithelium was hypertrophied and surrounded for the most part in ring form an atrophied or still relatively normal part of the epithelium. The changes were most frequently found at the margin of the squamous and glandular epithelium where the processes first appeared to be atrophic and degenerative, but later became hypertrophic, apparently as the result of infection. In a large series of vitamin A deficient animals, Arons and van der Rijst[67] found 64% had changes similar to ulcers in the squamous epithelium of their stomachs, which these authors thought were probably non-specific. Pappenheimer and Larimore[68] had previously stated that similar gastric lesions were possibly due to the swallowing of hair. Manville[69] found that white rats on a vitamin A deficient diet developed gastric ulcers and peptic erosions. The incidence varied from 60 to 100%, depending on the amount of vitamin A in the diet. In these animals there was also a reduced amount of mucus secreted by the stomach (method of determination not stated). The pH of the normal stomach they found to be 3.4; in the stomach with ulcers it was found to be between 2.5 and 3. When Fogelson's mucin was fed, it seemed to have some beneficial effect on the stomach, but it did not prevent death from the vitamin deficiency. Incidentally, a high incidence of microscopic gastric ulcers has been found in rats fed a vitamin B_1 deficient diet[70] and about 25% of a series of 75 guinea pigs fed diets deficient in vitamin C developed macroscopic ulcers in their stomachs.[71]

Turner and Loew[72] noted gastric dilatation in their monkeys which had died from A avitaminosis. Manville[45] reported that after about 2 months on an A deficient diet the rat's mouth, large bowel, rectum and feces became drier, probably due to a lack of glandular secretion, and pH of the saliva changed from the normal 7.4 to 6.6. Debré, Busson and Simmonet[73] found hemorrhages into the stomach, intestines and bladder in their A deficient rats and the extent of the bleeding increased with the severity of the deficiency.

Even as little as 3 weeks on an A free diet is usually sufficient to cause changes in the intestinal tract which are visible to the naked eye, according to the recent work of Richards.[5] She observed with great frequency keratosis and ulceration in the squamous part of the stomach, and pittings, hemorrhagic points and even ulceration in the glandular part. These changes as well as those found also in intestinal tract (see below) this author thinks are responsible for most of the decreased rate of growth in such animals.

A good many years prior to this Cramer[74] (1923) had found marked atrophy of the villi with necrosis of their tips in the lower ileum of animals fed diets lacking the fat soluble vitamins, when compared with controls fed either a barely adequate or a vitamin rich diet. These changes he thought would lead to decreased absorption of the food. This same author, with Kingsbury,[75] found that in this deficiency the mucous glands of the intestine atrophy and there is of course a decrease in the amount of mucus. This favors bacterial multiplication, and he observed that the bacteria which normally are almost restricted to the central lumen, in these avitaminotic rats penetrate between the villi into the crypts of Lieberkühn and into the mucous glands of the cecum, which they fill and where they proliferate. Wolbach and Howe[7] noted

a very slight atrophy of Brunner's glands. De Ruyter has recently also found atrophy of the mucous glands, and in addition the disappearance of the goblet cells in the intestine. Some years ago, MacKay[76] found that when kittens were kept on diets deficient in the fat soluble vitamins they developed diarrhea and abdominal distention and the intestinal wall was found at autopsy to be very thin.

Several authors have found that diarrhea commonly occurs when animals are fed such diets. Nicholls[56] and also Pillat[52] observed diarrhea in human cases of keratomalacia, where it came on some time after the eye changes began. Wolfe and Salter[23] observed it in mice, Hart *et al.* in cows,[26] Turner and Loew[72] in monkeys, and Gudjónsson[46] in a few rats at the terminal stage. In the monkeys it was very severe and ended in death, and at autopsy the intestines showed marked enteritis. Tilden and Miller[22b] regularly found that monkeys developed diarrhea and colitis on A deficient rations. When the monkeys were examined after death a few showed gross ulcers in the colon, more showed microscopic ulcers and severe colitis, and a few showed less severe lesions. Two monkeys showed no changes in the intestine. On the other hand, Hetler[22a] observed colitis in only 3 of his 27 A deficient monkeys, and 2 of these had intestinal ulcers with inflammation or edema of the intestinal mucosa. He thinks that the colitis observed by others in monkeys may have been due to the use of an irritating diet. The monkey apparently is prone to develop diarrhea. Seifried[18] observed intestinal catarrh and inflammation in adult hens fed A free diets.

Richards[5] has recently reported a strikingly high incidence of cecal inflammation in rats on A deficient diets. Ulcers of the cecum were also quite common, as well as inflammation of the duodenum and the rest of the small intestine. Diarrhea, especially in the later stages, was not infrequent. There was apparently no epidemic of enteritis and the controls were unaffected. One would infer that infections had been set up in the intestinal mucosa which had been rendered more vulnerable by the food deficiency. Richards' report is based on large series of rats and should be repeated by other investigators. Green and Mellanby[77] had an epidemic of enteritis during the course of their experiments and their vitamin A deficient rats were very susceptible, 21% of them dying.

Ackert and his collaborators[78] noted more material than usual in the intestines of their A deficient chickens, which suggested sluggish peristalsis. Gross,[79] by means of feeding charcoal to rats and identifying it in the feces (a method which the present author found unsatisfactory), found that material passed more rapidly than normal through the intestines of A deficient rats. Seidmon and Arnold[80] demonstrated that the intestinal tract of A deficient rats was more permeable to bacteria, as determined by feeding the organisms and culturing several organs after ½ to 1 hour intervals than was that of adequately fed controls.

Working with young children and infants, Rowntree[81] demonstrated that much vitamin A is excreted in the feces. In 2 of the infants fed a diet low in vitamin A, the excretion exceeded the intake. Perhaps the excretion of vitamin A by the intestinal mucosa may provide the cells with this factor, so that they locally do not suffer from a lack of

this factor and do not show metaplasia. No vitamin A was found in the urine even though generous amounts were fed. Von Drigalski[82] found vitamin A in the feces of rats when they were fed it in excess. In human beings he did not find it in the feces.

Sweet and K'Ang,[58] who carried out 17 autopsies on Chinese patients suffering from avitaminosis A, found in 5 that the esophagus showed hyperkeratosis (like epidermis). The submucosa was infiltrated with a moderate number of lymphoid cells and a few mononuclears. The digestive tract otherwise was normal.

Urinary System. According to the work of Wolbach and Howe the epithelium of the renal tubules showed no metaplastic change. Mendel[15] stated that the cells of the renal tubules seem to become calcified in some instances when rats are deprived of vitamin A for long periods. De Ruyter[9] has recently published a photograph of such calcified epithelial cells. van Leersum,[83] using rat diets which were probably deficient in both vitamins A and D, found calcium deposits very commonly in the kidney tubules. This finding was very rare in the adequately fed controls. Davis and Outhouse[84] fed their rats a diet which was partially deficient in vitamin A and probably free from vitamin D. They found cloudy swelling of the parenchyma of the collecting tubules, which was especially well seen in the second generation raised on this diet. Sometimes an albuminous precipitate was seen in the tubules. The bloodvessels were also congested. Gross[79] reported that in vitamin A and D deficient rats there was a greater incidence of vacuolation of the cells of the convoluted tubules near the pyramids and more marked congestion than normal. In a series of only 7 rats which were fed an A and D free diet, Frontali[85] found 4 with macroscopic abscesses, 2 with microscopic abscesses and 1 with perivascular hemorrhages in the kidney substance. Other investigators have not as yet confirmed this work. Chu and Murphy[86] state that in the early stages of vitamin A deficiency their rats did not show any reduced kidney function as measured either by the excretion of creatinin or by specific gravity determinations on the urine.

Quite a number of detailed studies have been made on the changes in the kidneys of chickens subsisting on suitable A free diets. Elvehjem and Neu[87] found that in such birds many of the renal tubules were dilated with urates and the whole kidney seemed to be filled with this material. The blood uric acid was raised, probably because of the kidney damage. There was always slight nephrosis and occasional areas of parenchymatous degeneration, mostly in the proximal convoluted tubules. The distal portion of the collecting tubules and the ducts of Bellini were considerably dilated. Some of the tubules contained leukocytes, giant cells and cellular débris, others considerable colloid material. Practically all the sections showed hyalin deposits in both arteries and glomeruli. Birds do not destroy uric acid and convert the greater part of the urea into uric acid for elimination. Beach[88] reported similar gross changes. Capper[89] and his co-workers found that chickens dying of vitamin A deficiency showed white, powdery deposits, apparently of urates, around the heart, liver and other organs, which agricultural experts diagnosed as visceral gout. Emmett and Peacock[90] reported similar findings and also that the kidneys were usually very pale and marked with a network of very fine

white lines, which were urate filled tubules. These workers, particularly Elvehjem, have demonstrated clearly that severe vitamin A deficiency caused definite pathologic changes in the kidneys of chickens. Similar intensive studies on the rat would be of interest.

Many authors have described metaplastic changes in the kidney pelvis of animals and even of man. Tyson and Smith[91] noted that these changes might appear early, even preceding those in the respiratory tract. They found that the epithelium first was piled up (hyperplastic) and the subepithelial tissue infiltrated with neutrophils. The epithelium later became keratinized. Harris and his co-workers[92] also described hyperplasia in the pelvis epithelium. Another frequent site of hyperplasia in the metaplastic epithelium is at the base of the tongue. Rats fed vitamin A free diets commonly develop pyelitis. Richards, for example, found that 45% of 64 rats fed such diets for 5 to 11 weeks developed such infections.

Metaplastic changes in the bladder epithelium are also common. Arons and van der Rijst[67] state that the changes always begin at the urethral orifice. If the rat is kept on the diet long enough, one-third to one-half of the bladder is affected, and later all of it. The keratinized epithelium shows verrucose thickenings. These authors found that these epithelial changes sometimes occurred without associated infections. Harris and his co-workers[92] thought that they had possibly found slight metaplasia without infection sometimes in the sublingual and submaxillary gland. These processes were, however, very usually found together and the infectious process never preceded the metaplastic. Frontali found epithelial pearl formation in the metaplastic epithelium of the bladder and, in his rats, cystitis was even more common than pyelitis. Bliss and his associates[93] found that if rats were fed diets lacking only vitamin A their bladders became distended and badly congested and some abscesses were found in the bladder walls.

Fujimaki[94] and also Higgins[95] state that the urine of rats fed vitamins A and D deficient diets becomes alkalin. If the missing vitamins are added the urine becomes acid again. It has been suggested that the alkalinity is due to infection with organisms, *e. g.*, staphylococci, streptococci or *B. proteus-ammoniæ*. The latter is known to convert urea into ammonia and carbonic acid, which would probably explain the more alkalin reaction. However, Higgins found alkalin urine regularly even before infections were demonstrated. van Leersum[83] reported that the urine was acid and he rarely found cystitis, or bacteria in the urine. Hematuria was, however, fairly common. Further simultaneous measurements of the urinary pH and accurate bacteriologic tests under such dietary conditions are indicated. Possibly some of the beneficial urine acidifying effects of ketogenic diets may be due to their high vitamin A content.

Considering the exfoliation of epithelial cells which may occur in either the pelvis of the kidney or the bladder, it is not surprising that several authors have noted an increase in the epithelial cells in the urine in human cases of keratomalacia.[62, 96] Chu and Murphy[86] also noted that 88% of a series of rats suffering from early vitamin A deficiency had increased numbers of epithelial cells in the urine.

The question of the relation of vitamin A to urinary calculi is at present in an unsettled state. As a short but comprehensive review on

the subject has recently appeared in the *Journal of the American Medical Association*,[97] this discussion will be brief. It is true that a good many of the authors who claim to have produced calculi in rats by a lack of vitamin A have as a matter of fact used diets deficient in vitamins D and C as well. However, as the rat can apparently synthesize vitamin C, it does not need this in its diet. As to the lack of vitamin D, Bliss and his co-workers[93] demonstrated that a diet deficient in vitamin A alone was just as effective as one lacking both vitamins A and D for the production of calculi. If vitamin A alone was added to the A and D free diet, calculosis did not occur. Also Higgins[95] found that diets deficient in vitamin D alone did not give rise to calculosis. It therefore seems reasonable to suppose that the associated deficiency of vitamin D has no effect, and that vitamin A is the important factor. Also Arons and van der Rijst found that 13% of their rats developed vesical calculi when they were fed a diet deficient only in vitamin A. The problem of lithiasis is further complicated by the fact that if excessive phosphates or especially calcium salts are added to the diet the incidence of stones increases markedly.[67] In addition McCarrison[98] showed that a diet devoid of fat-soluble vitamins and high in calcium (also low in good proteins) frequently caused calculosis. The addition of neither phosphates nor vitamin A alone prevented the formation of the stone, but if both these substances were added simultaneously no stones were formed. In other words, McCarrison showed that urinary stones could be formed when vitamin A was present in the diet. Other investigators[99, 100] have also found this to be the case. In 2 cases the Ca/P ratio in the diet was abnormally high,[98, 99] and in the third an excess of magnesium carbonate was fed.[100]

When the rats are fed diets deficient in vitamins A and D, the stones are almost always composed of phosphates of calcium and magnesium with a little organic material and possibly traces of oxalates of potassium and sodium. In man the problem is more complicated as several varieties of stones (urates, phosphates, etc.) may occur. As a general rule rats must be kept on the deficient diets for long periods, with short intervals on a normal diet to keep them alive, before the stones appear. The cystic stones appear first, later followed by renal stones and finally by stones in the bile ducts.[94] The latter are formed largely of cholesterol and pigment. Emiliani and Bazzocchi[101] reported that 75% of their guinea pigs fed an A deficient diet developed biliary calculi. When a vitamin B deficient diet was used, no biliary calculi were formed.

No adequate theory has been proposed to explain why a deficiency of vitamin A leads to the formation of urinary stones. Some of the factors involved may be as follows:

1. The sloughed off keratinized cells may provide nuclei for the stones.
2. The drainage of the urine may be interfered with, due to epithelial proliferation in the ureters or urethra.
3. This stasis of the urine may favor infection. Infection very commonly accompanies calculosis.
4. The alkalin reaction of the urine, due perhaps to bacterial changes, may allow the salts in the urine to be precipitated out of solution.

Genital System. *In the Male.* In 1925, Wolbach and Howe[7] reported that in rats which had been fed a vitamin A deficient diet

for some time, the testes were only about half their normal size. About a year earlier Gross[79] had noted the same atrophy. However, early in the course of the deficiency the testes showed marked edema. Thatcher and Sure[102] only occasionally observed edema beneath the capsule and extending slightly between the glands. They noted in addition that general or local atrophy of the tubules was common. Wolfe and Salter[23] found that in mice the testes were small, soft and watery when cut. Manville[45] found the seminal vesicles underdeveloped in his vitamin A deficient rats.

Metaplastic changes in the epithelium of the epididymus, prostate, seminal vesicles and Cowper's glands have been described in both the rat[7] and the guinea pig.[24] Similar changes in the last three organs were also found in the mouse.[23] In man, Sweet[58] observed metaplasia of the prostate in 1 of 10 cases of keratomalacia. Abscesses may later occur in the seminal vesicles and prostate and preputial glands according to Arons and van der Rijst.[67]

Goldblatt and Benischek[16] found atrophy and degeneration of the germinal epithelium and Wolfe[23] described somewhat similar changes in mice. A really detailed investigation was published by Sampson and Korenchevsky[103] in 1932. They described changes similar to those found in vitamin E deficiency with the formation of giant cells. However, from the excellent work of Mason[104a] which appeared in 1933, it appears that Sampson's diets were likely deficient in vitamin E as well as vitamin A. A deficiency of vitamin A seems to accentuate the need for vitamin E. In vitamin A deficiency only, Evans[104b] and also Mason found that the testes changes occurred before or at about the same time as xerophthalmia and frequently before any loss in body weight. The earliest change consisted in marked sloughing of the germinal cells into the lumina, with a consequent reduction in the tubule size. Often there were small numbers of deeply staining pyknotic cells visible. The epithelium seemed capable of slow cellular differentiation and sperm production for a considerable period of time in spite of the marked reduction in tubule size. The tubules usually contained from one to four layers of germinal cells, mostly spermatogonia and very immature spermatocytes with a few more mature cells attempting to produce sperms and a few poorly formed sperms. As the degeneration progressed spermatogenesis stopped, and in the final stage the picture was very similar to that of the last stage of vitamin E deficiency, although in the latter there is usually a more complete removal of the residual germ cells. These changes in the germinal epithelium are of course not those of keratinization.

The poor nutritive state of the animal probably results in the decreased production of the sex stimulating hormones of the anterior pituitary, which in turn leads to atrophy of the accessory sex organs.

In the Female. Wolbach and Howe found metaplastic changes in the epithelium of the oviduct and uterus in the rat[7] and guinea pig,[24] and such changes have been found in the latter organ in man.[51] The altered uterine epithelium may explain the frequently observed sterility in A deficient rats.[15] The cause may, however, be a partial or complete blocking of the oviduct with desquamated epithelium. Evans[105] found that about one-fifth of the copulations of A deficient females resulted in pregnancy, and that the young which were born were normal. When

pregnancy did not result, there was no evidence that implantation had occurred and in some cases where sections were made of the oviducts 1 to 3 days after copulation, degenerating ova were found which showed no signs of fertilization or cell division. Manville[45] and others also thought that fertilization and implantation often did not occur. Sure,[106] on the other hand, found evidence "by the resorption curve" and by the appearance of the uterine horns, that the rat fetus had been resorbed during gestation. One would suspect that this was due to an associated deficiency of vitamin E. It has been observed that the normal phenomenon of pseudopregnancy does not occur in vitamin A deficient rats, which suggests that there is some impairment in the internal secretions of these rats.[105] Hughes and his collaborators[25] regularly found that sows fed A deficient diets and bred before the onset of nervous symptoms always aborted or gave birth to dead young.

It is probable that no changes occur in the ovaries of rats fed vitamin A deficient diets, as Drummond,[102,107] Coward[108] and Thatcher and their co-workers have found. Opinion, however, is not unanimous on this question as Gross[79] found in the rat that more Graafian follicles than usual were degenerating, and in the guinea pig, Wolbach and Howe[24] consistently found atrophy of the ova and Graafian follicles. Further detailed studies of the ovaries of such animals would probably clear up the question.

In 1922, Evans and Bishop[109] observed that in female rats fed diets deficient in vitamins A and D the vaginal smears, which normally consisted of cornified epithelial cells only for about 30 hours during estrus, became persistently chiefly if not exclusively composed of these cornified cells. However, these workers observed that such animals continued to ovulate and to form corpora lutea irregularly or at intervals approximately normal. Evans[105] later studied this problem by observing the behavior of such females in the presence of normal males, by examining their ovaries for presence of ripe follicles, and by removing both ovaries and then examining the vaginal smears. At times when only cornified cells were present in the smear, the females did not copulate, and ripe follicles were absent. Also the continuous cornified smears appeared even when the ovaries were absent. In other words, these vaginal changes were unrelated to the ovary. The addition of vitamin D to the diet did not alter the reactions. Aberle[110] made sections of the vaginas of such animals and found that the peripheral cells of the vagina were cornified, and in many instances leukocytes were seen between the cornified cells. She also noted that at about the time the continuous cornified smears appeared, the vagina was very dry, and that the vaginal mucosa could not produce mucus even after the injection of excessive amounts of placental extract. In normal rats this treatment causes large amounts of mucus to be secreted. Mason[111] later reported that mucus production in the vagina ceased in these animals. In fact this author made the general observation that the ability of epithelial cells to produce mucin was lost in vitamin A deficiency, whereas that of producing keratin was increased. He suggested that vitamin A had some controlling influence on protein metabolism in the epithelial cells. He also noted that no preliminary atrophy occurred in the vaginal epithelium in these rats. The vaginal epithelium increased greatly in thickness, which fits in with the finding,

previously reported by Aberle,[112] of increased mitotic activity in this tissue in castrate rats. In the normal rat, at the approach of pro-estrus the superficial layers of the vaginal epithelium are nucleated, and these cells appear in the pro-estrus smear. Beneath this is a cornified layer which is shed during estrus. In the deficient rats the superficial layer becomes cornified, and the normally cornified layer becomes wider. It is less completely removed immediately after estrus, and this, plus the abnormal cornification of the deeper layers, leads to the appearance of cornified cells in the di-estrus smears.

Mason[113] also examined the vaginal smears of rats fed the A deficient diet and of controls whose weights were kept at approximately the same levels by feeding reduced amounts of a complete diet. He stained the smears supravitally with neutral red which enabled him to demonstrate the estrus cycles despite the abnormal cornification. The estrus cycles became definitely longer and irregular when the animals showed retardation or decline in growth, regardless of whether the deficient or restricted adequate diet was fed. The effect on estrus was therefore due to inanition only. However, the abnormal cornification occurred only in the rats fed the vitamin A deficient diet and was apparently the specific effect of this lack.

It has been stated that the appearance of continuous cornified vaginal smears is the first sign of vitamin A deficiency. This has not been found to be regularly the case,[109] although it may occur in some 40% of the animals before cessation of growth.[86] It does precede xerophthalmia, and as growth retardation is not a specific effect, it has been used as a means of testing for vitamin A. Turner and Loew[72] observed that after monkeys had been fed such diets for about 60 days their vaginal smears showed persistent cornified cells and the menses ceased. Hart[26] also observed that at the end of a very dry summer the cattle on a certain ranch developed night blindness, corneal ulcers, diarrhea and the non-recurrence of estrus after calving. Calves born late in the season died. The survivors recovered when green feed was available again. Manville[45] also noted lessening of the mammary secretions due to incomplete development and decreased function.

It has been found that 3 to 5 γ of carotene (pro-vitamin A) will cure the specific ophthalmia and cause slow growth, but the vaginal smears still remain abnormal.[114] If 10 γ is given, di-estrus smears appear within 1 week, and estrus within 2 weeks. That vitamin A is very essential for reproductive activity has also been shown by Manzi[115] who found that larger amounts of carotene were required by a pregnant guinea pig on a diet free of vitamin A to bring the pregnancy to a successful termination than for maintenance of a non-pregnant animal on the same diet.

Spleen. Several authors have made brief references to the changes occurring in the spleen in vitamin A deficiency. For example, Davis and Outhouse[84] found only very slight changes in the spleen, such as congestion and frequent dilatation of the venous sinuses, in rats which were fed diets partially deficient in vitamin A. Wilson and Du Bois[51] noted that the spleen of an infant that died apparently of this avitaminosis had splenic nodules with very pale centers, in which large mononuclear cells with abundant protoplasm were numerous. The same changes were noted in the mesenteric glands and Peyer's patches.

Gross[79] stated that his rats showed a great increase in thickened hyalin bloodvessels and pigment. Wolbach and Howe[7] noted a great diminution in the size of the spleen which was due to the depletion of the lymphoid cells and erythrocyte forming cells. There was, however, an increase in phagocytic cells laden with hemosiderin. They also remarked that the same changes were found in vitamin B deficient rats. These same authors later stated that guinea pigs showed no change in the size of the spleen, but it contained heavy accumulations of hemosiderin in the phagocytic cells. Blackfan and Wolbach[21] found hemosiderosis in the spleens of all the infants, apparently dying from this deficiency, that came to postmortem, and Sweet and K'Ang[58] found it in half their adult cases of keratomalacia. These investigators thought that the hemosiderosis, which occurred frequently in other conditions, was not a specific effect of the deficiency. Thatcher and Sure[102] reported that the spleen showed atrophy; Bliss *et al.*[93] that it was discolored and in most cases shrunken and infiltrated with fat; and Wolfe and Salter[23] that it was usually very dark and small.

A very detailed investigation was published by De Ruyter[9] in 1934, including excellent photographs of the histologic changes in the spleen. In early deficiency the spleen is macroscopically normal. Microscopically, the Malpighian bodies are easily made out and it is seen that the central area, which is much wider than usual, is composed of many large, markedly phagocytic cells and a few lymphocytes. The outside zone is smaller than usual and contains a smaller number of small lymphocytes and a larger number of large and medium-sized lymphocytes and histiocytes. At the periphery of the spleen the cells are larger and swollen and show mitosis. Also numerous free histiocytic cells and marked phagocytosis is seen here, which would suggest that there was stimulation rather than atrophy, although the small lymphocytes have partially disappeared. This deficiency of lymphocytes is also evident in the atrophy of the Peyer's patches and of the solitary follicles, and in the white blood picture.

In marked vitamin A deficiency, the spleen is very small and thin and the Malpighian corpuscles can hardly be made out. On high magnification it is seen that in the central areas of the corpuscles there are large swollen reticular cells, numerous small and medium-sized lymphocytes, occasional free histiocytes and a number of large macrophages full of blood breakdown products. The germinal center is therefore in an active phagocytic state. Lymphocytes are very scarce in the next layer. The periphery of the spleen appears inactive and no evidence of mitosis is seen. In some places remains of red blood cells and a few intact red cells are seen. The histiocytes are rare and where they are found they are laden with detritus and pigment.

When trypan-blue was injected, the ability of the reticulo-endothelial cells of the spleen to accumulate it was very markedly reduced.

Rydh-Ehrensvärd and Schmidt[116] reported that the guanase activity of the spleen was lowered in rats on an A free diet and also that the activation period of the enzyme was also changed. Carotene feeding raised the guanase content of the spleen and restored the activation period to normal.

Lassen[117] showed that rats fed vitamin A and also A and D deficient diets were considerably more susceptible to *B. avtrycke* infections

whether they were inoculated *per os*, subcutaneously, intravenously, or intraperitoneally, than were normal controls. With the last three methods, the effect of the possibly increased permeability of the mucous membranes is ruled out. With oral infections he found that in the normal controls the bacteria were localized for the most part in the Peyer's patches and mesenteric glands, with some extension to the liver and spleen. In the avitaminotic animals the liver and spleen were regularly involved and a fatal bacteremia followed. These results might be explained on the assumption that the reticulo-endothelial system was not functioning efficiently.

Crimm *et al.*[118] also noted that after the injection of *B. typhosus*, vitamin A deficient animals had a more persistent leukocytosis than did either the controls or the moderately deficient animals. It would appear then that the ability of the reticulo-endothelial system to fix and dispose of foreign protein is reduced in this deficiency.

Liver. Several authors have reported that no changes occur in the liver of vitamin A deficient animals; for example, Wolbach and Howe[24] using guinea pigs, and Wolfe *et al.*[23] with mice. Davis and Outhouse[84] also found that the livers of partially deficient rats were normal. On the other hand, Gross[79] reported great congestion in the liver, and Wolbach and Howe[7] noted diminution in size, which they thought was due to the absence of stored fat and glycogen. These investigators used white rats. Thatcher and Sure[102] found in about one-third of their deficient rats that there was fibrosis about the portal spaces, and infiltration with eosinophils and small lymphocytes. Only one of their controls showed a similar but less marked reaction. De Ruyter[9] later independently reported fibrosis in these same areas. Bliss and his collaborators[93] noted that the liver was discolored and frequently shrunken and infiltrated with fat, and Blackfan *et al.*[21] and also Sweet *et al*[58] described hemosiderosis in the liver as frequently as in the spleen.

De Ruyter[9] also gave a detailed description of the liver changes. Macroscopically only 24 of the 178 livers examined showed changes which could be ascribed to the deficiency, such as diffuse swelling and a yellowish-brown color. Microscopically, of 42 livers examined only those in the very early stages of the avitaminosis showed no changes. In the others, the liver cells contained either large or small vacuoles, apparently of fat. The nuclei were sometimes pyknotic and sometimes did not stain well. In the early stages the fat appeared only in the cells about the periphery of the lobule, but later these changes were generalized. The glycogen disappeared from the liver cells. The fibrosis around the bile ducts occurred only rarely. Changes in the Kupffer cells, which occurred early and regularly, consisted in swelling, deposition of fat and pyknosis of the nuclei. When trypan-blue was injected the Kupffer cells absorbed it very poorly. Leber,[119] in 1883, described a human case of keratomalacia in which the liver was fatty.

Saiki[120] tested the excretory functions of the liver of rats and monkeys fed normal and vitamin A and D deficient diets by injecting Azorubin S intravenously and then determining how soon it was excreted by the bile and how long the bile contained it. In the deficient animals the dye was excreted much less rapidly, although the time of appearance in the bile was not much altered.

Drummond and his co-workers[121] injected a colloidal solution of

carotene intravenously into cats. They found that the greater part of it was immediately absorbed by the liver where it was found exclusively in the Kupffer cells. It is well known that in the normal animal the main store of vitamin A is in the liver.

Blood. As regards the number of red blood cells, several authors (Happ,[122] Turner,[123] Falconer[124]) state that this is unaltered in vitamin A deficiency; Damianovich[125] found it reduced. Cramer, Drew and Mottram[126] reported that in the early stages there was no constant difference, but that in the advanced stages anemia was present. Koessler and his co-workers[127] were able to cause a blood picture similar to that of pernicious anemia by feeding deficient, adequate, deficient and finally adequate diets. This has apparently not been confirmed by other investigators. Davis and Outhouse[84] gave their rats a diet low in fat soluble vitamins and found marked anemia in the second generation. Frank[128] has recently reported a decrease of 25% in the red cell counts of rats fed a diet deficient in vitamins A and D and consisting of oats 40, extracted casein 5, dextrin 52.5, NaCl 1, and $CaCO_3$ 1.5. It is possibly also a little low in the vitamin B complex. The blood was obtained by heart puncture. Mouriquand and his co-workers[129] also report anemia in vitamin A deficiency.

Whether the white blood count is altered in vitamin A deficiency is still an open question. At least three authors[118, 126, 130] have reported no change. On the other hand, Falconer[124] found a rise of about 20% and Turner and Loew[131] noted that from the stage of moderate xerophthalmia on, there was a progressive and marked rise in the white blood count. One would associate this with the frequent epithelial infections. Frank,[128] however, states that the leukocyte count is decreased in A deficient rats. Children with xerophthalmia on the contrary had a much increased white blood count, which was reduced about 50% after a short time on a high vitamin A diet. Several authors[128, 130, 131] have noted that the per cent of neutrophils increases, with a corresponding decrease in the lymphocytes. One of these investigators,[131] however, found that this did not always occur, even in advanced deficiency. Crimm and Short[118] have recently made the interesting observation that the percentage of senile granulocytic cells is increased. Apparently then a lack of vitamin A inhibits the formation of these cells. If vitamin A were given to one of these deficiently fed animals, there was marked increase in younger cells.

There is also considerable variation as regards the platelet counts. Kugelmass[132] and Frank[128] found them unchanged. Falconer[124] and also Bedson and Zilva[133] found a reduction of about 20%, which the latter authors did not consider specific. In the earlier work, Cramer and his associates[126] found a marked thrombopenia, which they thought was caused by the platelets adhering to bacteria which were frequently present in the blood stream. Later investigators rarely were able to culture bacteria from the blood.[131]

Falconer[124] found no definite change in the hemoglobin, whereas Frank[128] reported a decrease of 27%. Falconer[124] also stated that the blood volume was reduced.

In rats, Kugelmass[132] found the fibrinogen content of the blood markedly lowered and the bleeding time prolonged. In similar animals Frank[128] found the fibrin content much reduced, the clotting time

increased, and the bleeding time at least doubled. He thought that these alterations were due to degenerative processes in the liver. In 2 infants suffering from xerophthalmia he found that the bleeding time was not increased although the plasma fibrin was down considerably. Simola[134] noted a much increased clotting time and much reduced lipase content in the livers of A-avitaminotic guinea pigs.

According to Binet and Strumza[135] the recovery of dogs from anemia due to bleeding is much helped by carotene *per os*. No vitamin A is found in the red blood corpuscles of the dog, but only in the plasma.

Teeth. Smith and Lantz[136] investigated the gross changes occurring in the incisor teeth of rats fed vitamin A free diets. At about the time that growth ceased and early signs of eye infection occurred, the teeth gradually lost their normal orange pigment and luster. They became short and blunt, and at death were found to be very friable. Measurements showed that the tooth growth was markedly retarded, in fact almost inhibited completely as death from vitamin A deficiency approached. If cod liver oil was given to the vitamin A depleted rats which had shown the above changes, the teeth grew normally again and regained their normal appearance and hardness. These authors also determined the percentage of ash, calcium and phosphorus in these teeth and those of controls fed the diet plus cod liver oil. The teeth of the rats fed the deficient diet contained 2% less ash, 4.4% more calcium and 0.8% less phosphorus, and it is suggested that less calcium was deposited with the phosphate radical and a larger proportion as the carbonate or in some other combination, which possibly explained the increased friability. Wolbach and Howe[137] noted the same changes, but thought that the loss of the normal orange pigmentation and the acquisition of the chalky white appearance were due to the loss of the enamel which is pigmented, and to a change in the composition of the dentine. Gudjónsson[46] had previously found the teeth of A deficient rats more friable than those of normal animals.

Shibata,[138] in an article that was apparently poorly translated into English, described in 1931 the appearance of the teeth of albino rats fed such deficient diets. They showed abnormal formation of the enamel, dentine and cementum, and atrophy and abnormality in the enamel organ, dental pulp and root membrane tissue. The incisors were erupted late and there was increased cornification of the epithelium of the gums. Simola[139] found marked histologic changes in the teeth, particularly in the odontoblasts and pulp tissue.

In 1933 Wolbach and Howe[137] published an excellent account of the changes produced in the incisors of rats and guinea pigs by diets deficient in vitamin A. The first changes appeared in the enamel organ, which is just outside the enamel and mostly on the labial side. It consists normally of an inner layer of higher columnar ameloblasts and outside this are small epithelial papillæ separated by vascular connective tissue. The papillæ first atrophy and the connective tissue becomes less vascular. The ameloblasts become smaller, then granular and finally disappear, and are replaced by two rows of flat cells, probably arising from the stratum intermedium. In very late stages of the deficiency these develop numerous layers of flat cells and may be keratinized. Deposits of calcium commonly appear in the connective tissue between the papillæ in the late stages in the guinea pig, but are

quite rare in the rat. These later take on the appearance of bone in the guinea pig.

At the same time as these changes are occurring in the enamel organ, the odontoblasts, which form the inner layer of the dentine, show atrophy. In the rat the odontoblasts on the labial side survive much longer than on the other sides, and as a result the dentine on this side is very much thicker than elsewhere. In the guinea pig, all the odontoblasts atrophy at the same rate. In the rat, when the atrophy is complete, the inner surface of the dentine is bounded by cells undistinguishable from the rest of the pulp cells. In the depths of the pulp small areas of osteoid tissue are frequently found in the late stages of the deficiency. Sometimes small glandlike clusters of ameloblasts are found within folds of thin dentine. These ameloblasts and also odontoblasts that have lost their polarity, probably because the normal ameloblasts have atrophied, form deposits of dentine-like material.

In the guinea pig the changes were similar except that the odontoblasts did not completely atrophy, spicules of dentine grew into the pulp, and the cementum which resembled bone was thicker and showed small outgrowths at intervals on its outer surface.

From the study of the teeth of adolescent children who were blind as the result of xerophthalmia in infancy, Bloch[63] concluded that vitamin A had no effect on dental caries or formation.

Previous mention (see p. 413) has been made of the changes which M. Mellanby found occurring at the gingival margins. In addition, she found that the epithelial attachment to the poorly calcified enamel is often less perfect. It normally occurs at the amelo-cement junction, but tends to extend rootwards in animals fed diets low in vitamin A. Also the connective tissue of the ligaments may be less well defined.

Recently M. Mellanby and King[32] have reported that in the teeth of puppies fed diets deficient only in vitamin A, the enamel is abnormal in color and texture, but no definite changes were seen in its minute structure.

At least three reports[21, 140, 141] have been published on the changes in bone as the result of deficiency of vitamin A. Probably, as these authors state, the changes are non-specific and are due to inactive osteogenesis, which would be expected from the stationary or declining weight and arrested growth.

Other Tissue Changes. Several authors[7, 24] have noted that the fat disappears from adipose tissue, even when non-vitamin A containing fat is present in the diet. In the rat,[7] clinical signs and microscopic changes do not occur until the bulk of the stored fat has disappeared. Guinea pigs,[24] on the other hand, showed advanced epithelial changes when considerable fat was still present.

No mention has been made of the changes occurring in the eye as they have been thoroughly described by numerous authors.[50, 52, 64]

Discussion. It is possible that vitamin A with its 5 unsaturated bonds may play an important rôle in the maintenance of a favorable oxidation-reduction potential within the body cells. Joyet-Lavergne[142] has shown that either oxidation or reduction reactions can occur on the surfaces of the mitochondria or nucleolus. He maintained conditions as nearly normal as possible and let substances which changed color with oxidation or reduction penetrate into the living cells, which

he was meanwhile observing under the microscope. In a later study he used an antimony trichlorid solution.[143] A blue reaction (very probably due to vitamin A) was consistently seen on the mitochondria of a great variety of animal and plant cells. The intensity of the blue color varied in different cells, being very intense on the mitochondria of hepatic cells and very weak in the salivary gland cells of a species of insects. If a nucleolus was present it became blue also. In the livers of sea fish, lumps of pale blue were also seen in the cell cytoplasm, often in contact with the mitochondria, and the author suspects that the mitochondria convert other materials into vitamin A which is stored as a reserve in the liver cytoplasm. The vitamin A in the mitochondria could be responsible for the oxidation occurring in the solutions used in the earlier experiments. No detailed description of the author's method was given in these articles. If these findings can be confirmed they will be of great interest.

Oppenheimer[144] suggests that vitamin A or carotene acts as an oxidation catalyst by taking up oxygen at its numerous double bonds and then giving it up again to the substance to be oxidized. Franke[145] showed that the power of oleic and linoleic acid to take up oxygen was doubled by the presence of carotene, which lost its color in the process. Vitamin A, and other carotinoids which could not replace vitamin A in the animal's diet however, had the same property.

Summary. 1. It is well known that a deficiency of vitamin A causes columnar and other types of epithelium to be replaced by squamous keratinized epithelium.

2. In young animals fed vitamin A free diets, it has frequently been shown that the fibers, especially those in afferent tracts or nerves, show degeneration of the myelin sheaths. The nerve cells of these fibers also frequently show degenerative changes. It seems quite possible that these changes in the sensory nerves may be responsible for the epithelial metaplasia.

3. It appears that in light adapted eyes vitamin A, but no retinen, a component of visual purple, is present; in dark adapted, retinen is present, but only a trace of vitamin A. In intact eyes, visual purple is regenerated from vitamin A, some of which is lost in the process.

4. In human beings, several authors have described papular eruptions due to the plugging of hair follicles with cornified material, with atrophy of the sebaceous and sweat glands. This is often associated with other evidences of vitamin A deficiency.

5. Hyperkeratotic changes associated with either ulcers or papillomata have been found by at least six investigators in the squamous celled fore-stomach of rats. Inflammatory changes in the cecum and elsewhere in the intestine may possibly be caused by this deficiency.

6. In the chicken, degenerative changes in the kidney epithelium associated with the deposition of urates in the tubules have been found. A prolonged deficiency of vitamin A frequently leads to the formation of urinary stones. If the Ca/P ratio in the diet is abnormal, the incidence of calculosis increases.

7. A typical series of changes occurs in the male germinal epithelium, finally leading to the cessation of a spermatogenesis.

8. In the female, the cells in the vaginal smears which are normally found at the various stages of the estrus cycle are replaced continuously

or almost continuously by cornified cells. This is apparently not associated with changes in the ovary.

9. According to recent work, the spleen in early vitamin A deficiency shows a decrease in its small lymphocytes and an increase in the phagocytic cells, larger lymphocytes and histiocytes. Later there is marked atrophy, although the germinal center still shows active phagocytosis. The absorption of trypan-blue is markedly reduced. Other evidence suggests a reduced efficiency of the reticulo-endothelial system.

10. Except in the very early stages, the cytoplasm of the liver cells contains vacuoles of fat and the nuclei show degeneration. Similar changes, with that of swelling in addition, were regularly seen early in the Kupffer cells. These findings need further confirmation.

11. It is likely that there is a relative decrease in the lymphocytes and a reduced fibrin content in the blood.

12. In the teeth, marked changes including atrophy of ameloblasts and odontoblasts and the appearance of osteoid tissue in the pulp occurred.

ELIZABETH CHANT ROBERTSON, M.D.

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HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

KENNETH F. MAXCY, M.D.,

PROFESSOR OF PREVENTIVE MEDICINE AND PUBLIC HEALTH, UNIVERSITY OF MINNESOTA, MINNEAPOLIS, MINN.

CHANGING CONCEPTIONS OF THE PREVENTION OF ACUTE ANTERIOR POLIOMYELITIS.

Mode of Transmission.—Regarding conditions of transmission, certain facts seem to have been well established by experimental studies and epidemiologic observations. The disease is caused by a filterable virus which enters through the nose, and leaves through the nose or respiratory tract. Transmission is effected through the respiratory route by person-to-person contact, and the contact required is of the same order as that which is effective in other respiratory-borne virus diseases such as influenza, measles, chickenpox. The individual who is exposed to the virus, depending upon the amount of resistance developed, may harbor the virus temporarily (*a*) without symptoms—a "carrier" state; (*b*) with a mild illness and symptoms of indefinite character—Frost's "possible abortive" cases; (*c*) with symptoms sufficiently developed to be characteristic and recognizable by those familiar with the syndrome, although the spinal fluid may be normal—Frost's "probable abortive;" (*d*) with characteristic clinical course and positive spinal fluid findings, but without the occurrence of demonstrable paralysis—"frank abortive" or "non-paralytic" poliomyelitis; (*e*) with characteristic clinical course, positive spinal fluid findings, and any degree of paralysis from a transient muscle weakness to a total ascending paralysis of the Landry type—the typical paralytic poliomyelitis. These classifications are not mutually exclusive and merge

into each other.* *Because of the widely varying symptomatology and the lack of a dependable objective test, it is at present impossible to set up a satisfactory criterion of diagnosis that will include all cases of this disease.*

The ratio of carriers, mild and missed abortive cases in comparison with recognized abortive and paralytic cases is still a matter of speculation rather than of exact statement. Evidence already at hand is sufficient to indicate that although this ratio may be variable in different epidemics, in different geographic areas, and even in different seasons, the former far out-number the latter.[1,3,4]

Prevalence.—If it be accepted that these facts have been established, then it follows logically that:

1, Attempts to measure prevalence by means of morbidity reports are subject to a considerable error variable with the recognition of the milder forms of the disease. This can be partially overcome by separate rates based upon paralytic cases alone.

2, Attempts to measure the mildness of the disease in a given place and time by means of the ratio between reported "paralyzed" and reported "non-paralyzed" cases is in like manner subject to an imponderable error.

3, Attempts to measure the severity of the disease in a given time and place by means of official case fatality rates are, for the same reason, unreliable because of the variable number of abortive and non-paralyzed cases included in the "total cases."

Careful epidemiologic field studies with definitions and methods stated as clearly as possible are necessary to obtain relatively dependable information. These observations must be kept in mind in reading official reports of recent outbreaks of the disease.[5–9]

Variability.—Even when due allowance is made for the errors mentioned above, there is considerable evidence to indicate that the manifestations of the virus vary in different areas, epidemics and times as Wickman pointed out some years ago. In parts of the United States it would appear that the disease has become clinically more apparent than formerly, that its symptomatology is not altogether constant, that in the past few years it has been somewhat less fatal in proportion to those frankly attacked than formerly,[3–5] that it is tending to shift its incidence toward higher age groups,[5,10–12] and that it may become highly infective even for adult groups.[3] It is also notable that recent epidemics have originated in areas of the southern part of the United States which hitherto have been largely free from such experiences.

Isolation and Quarantine.—If it be accepted that the conditions of transmission are essentially as outlined, then it also follows logically that the spread of the disease in human populations cannot be effectively limited by the isolation of recognized cases and their immediate contacts, no matter how rigid the restrictions imposed may be. This does not imply that such procedure should be abandoned nor that it does not in some degree restrict the spread of the disease to the immediate environment of a known case. It suffers from the same inadequacies

* Paul, Salinger and Trask[1] suggest that (*b*) and (*c*) be grouped together on the basis of suggestive symptomatology and negative spinal fluid findings, and that (*d*) be included with (*e*) as frank poliomyelitis. The practical objection to this proposal is that spinal fluid findings do not necessarily parallel clinical severity,[2,3,4] and lumbar puncture is not always an available or permissible procedure.

as does isolation and quarantine in the other respiratory-borne virus diseases, that is, the case is infectious for some days before the diagnosis is made, and unrecognized cases and carriers can spread the disease just as effectively as can known cases.

It seems then that exposure to the virus is probably inevitable for everyone sooner or later, just as it is with the virus of such diseases as measles, mumps and chickenpox. The preventive effort must be directed primarily *not toward reduction in spread, but to decrease the incidence of clinical attacks* with the concomitant risks. Fortunately in poliomyelitis the natural resistance of the vast majority of human beings to infection is sufficiently great *to achieve immunity without penalty.* In only one or two out of each thousand population exposed does the defense mechanism fail to the extent that paralysis results from the infection, and in only about one out of each five to ten thousand population or more is the paralysis fatal. It would seem that with only a little improvement the natural defense mechanism could be made adequate for a still greater proportion of individuals.

Efforts to accomplish this result have proceeded along three lines, namely, 1, temporary passive immunity conferred by convalescent serum, 2, active immunization by vaccination with attenuated or killed virus; 3, improvement in the defense barrier at the point of entrance in the nose by nonspecific means. A discussion of the present status of each of these procedures will be clarified if first a brief résumé be given of the present conception of the pathogenesis of the disease. For a complete review the articles by Fairbrother and Hurst,[13] Schultz,[14] and Faber[15] should be consulted.

Pathogenesis.—The virus is neurotropic. It grows in nerve cells and propagates along their axones. The site of implantation and initial multiplication is the nasal mucosa, and very largely, if not entirely, the olfactory epithelium high in the nose lining in the superior meatus and the corresponding part of the nasal septum.* This the virus must reach in order to establish an infective contact.

Having gained a foothold in the olfactory epithelium and established initial growth, it propagates by way of the axones to the olfactory bulb. From the bulb it makes its way along the olfactory tracts to the hypothalamus. As it progresses it dies out in areas previously infected. It is unable to reach the cerebral hemispheres or the cerebellum in quantities sufficient to be demonstrable. It finds a better opportunity to survive proceeding toward the brain stem and spinal cord. It makes its way from above downward[18] and may be demonstrated at successive

* This does not preclude the possibility that the virus may enter by other pathways, but the evidence strongly supports the idea that it is the natural and usual portal of entry. It seems quite unlikely that it can become implanted upon the intact mucous membrane of the gastro-intestinal tract and make effective contact into the nerve supply unless local injury predisposes the area.[16,17] Bulbar paralysis in cases of poliomyelitis following tonsillectomy may be explained as due to effective contact of the virus with nerve endings in the injured tissue. In this connection it is interesting to note (Leake[6]) that in cases of poliomyelitis following the use of the Kolmer's vaccine in each instance in which the site of the injection and the site of the first paralysis is known, the latter occurred either in the limb injected or in the corresponding limb of the other side. In other words, the cells of the spinal cord first involved were at the same level as the injection, suggesting that the virus traveled directly by way of the nerves which supplied the area into which the injection was made.

levels in the anterior and posterior horns and even in the intervertebral ganglia.

It shows a particular affinity for the anterior horn cells upon which it exerts its maximum toxic effect. The perivascular cuffing of the small bloodvessels follows. The systemic invasion suggested by lymphatic hyperplasia is a secondary phenomenon due to the peripheral distribution of the virus out from the central nervous system probably along nerve pathways.

Although this conception of the pathogenesis of the disease rests largely upon observations made upon monkeys, it is consistent with knowledge derived from the study of other virus diseases and with the clinical, pathologic and epidemiologic manifestations of poliomyelitis in human beings.

Convalescent Serum.—The earliest attempts to prevent or check the progress of paralysis in human cases involved the therapeutic use of convalescent serum. It was based upon the observation that such serum, and indeed the serum from a considerable percentage of the adult population who have, to their knowledge, not had poliomyelitis, is capable of neutralizing the virus *in vitro*. Since at this time it was held that the virus gained access to the central nervous system through the blood stream and spinal fluid, with localization in the meninges, it was reasoned that if the serum were introduced sufficiently early in the course of the disease it would exert a protective effect. Flexner and Lewis,[19] 1910, and Flexner and Amoss,[20] 1914–1917, reported that if the intracerebral injection of a monkey is sufficiently small in dosage and followed within 24 hours by convalescent serum intraspinally (2 cc.) one may in some instances prevent the development of symptoms.

Upon the basis of this very limited theoretic and experimental background, the use of convalescent or adult serum was advocated *in the treatment* of human cases and received extensive clinical trial. Injections of 10 to 20 cc. were usually made intrathecally at the time of the diagnostic lumbar puncture, frequently supplemented by additional amounts given intravenously and subcutaneously. It was evident that if the disabling sequelæ were to be prevented or ameliorated the treatment must be applied before nerve-cell destruction had taken place. Proponents of its use therefore advised that it be restricted to those cases in which it could be given in the preparalytic stage.

From a careful review of the results in a large series of cases treated by this procedure, Aycock and his collaborators in the Harvard Infantile Paralysis Commission (1928–1929)[21] confirmed the opinion expressed by many others on the basis of more limited clinical trial, that the amount of paralysis and mortality was significantly lower in the treated in comparison with untreated cases. It later appeared, however, that this difference was due to the fact that the treated cases were a specially selected group of preparalytic cases while the untreated were not. When the two groups were made as nearly alike as possible Kramer, Aycock, Solomon and Thenebe[22] and Park[23] found that the statistical advantage in favor of the treated group disappeared.

Schultz and Gebhardt[24] have recently reinvestigated the therapeutic value of specific immune serum in experimental poliomyelitis in the light of recent studies which indicate that from the very beginning of the infection the virus is intimately associated with neurones and that

once it is established in the nervous system it is propagated largely if not entirely along axonal routes. As a result of a series of carefully controlled experiments on monkeys they conclude that a highly potent virucidal (specific immune horse and convalescent monkey) serum injected by various routes one or more days after inoculation of the virus is without demonstrable value in the treatment of experimental poliomyelitis.

Evidence derived from both clinical and experimental trial therefore failed to establish the value of this procedure. It remained to ascertain whether it was possible to confer some degree of temporary passive immunity and protection upon human beings by the injection of convalescent serum *before exposure*, that is, prophylactically.

Opportunity was afforded by the unusual outbreak which occurred among the personnel of the Los Angeles County Hospital in 1934. Kessel, Hoyt and Fisk[3] gave prophylactic injections of convalescent and normal adult pooled serum to 892 employees and subsequently followed their attack rate in comparison with that of 3094 employees in the same institution who received no serum. Briefly stated there was no evidence to indicate that any protection was afforded. In fact the percentage attacked was higher among those who received the serum than among those who did not, due probably to the inclusion in the former group of a higher proportion of specially exposed persons.

Schultz and Gebhardt[25] investigated the question with monkeys. They administered immune (virucidal) serum of high potency by various methods and in varying dosage from a few hours to 2 or 3 days before the animal was experimentally infected. The results indicated that immune serum is far from being a dependable prophylactic agent. The authors cautiously conclude that a liberal amount of high titer immune serum may protect animals against small doses of virus by diminishing the amount on the olfactory mucous membrane free to initiate infection. Once infected, the serum-treated animals generally develop as extensive paralysis as do controls, indicating that once the virus becomes established in neurones it can no longer be effectively reached by the virus-neutralizing antibodies.

In view of this evidence it is clear that *convalescent or immune serum, even when prophylactically administered cannot be relied upon to confer even a temporary protection against infection.*

The Poliocidal Substance in Human Serum.—These and similar observations have brought to the fore the question of the nature and function of the virus-neutralizing substances. It is well established that they appear or are increased in the blood of individuals who have passed through an attack of the disease, in the blood of monkeys surviving experimental poliomyelitis and of monkeys vaccinated with virus emulsions, living or killed. It is also true that they appear in the blood of adults who give no history of a previous attack of the disease. Jungeblut[26] has suggested that while they may result from contact with the specific antigens, they may also be of heterophil nature, arising from experience with other antigens. Be that as it may, their presence in serum is not synonymous with immunity.

Schultz and Gebhardt[27] and others have demonstrated that monkeys immunized with virus emulsions and showing as a result virucidal properties in their serum can be readily infected by the experimental method.

The defense mechanism apparently depends primarily upon neuron susceptibility. True acquired active immunity requires some modifying action which results from active neural infection. This modification need not be associated with demonstrable virucidal antibodies in the blood. Such humoral antibodies as may make their appearance in naturally acquired active immunity may result from chance contact of virus with extraneural tissue and may therefore be entirely adventitious so far as true immunity is concerned. This would offer an additional explanation for the failure to prevent infection by the prophylactic injection of immune serum.

Active Immunity.—With the failure of the use of immune serum to prevent or protect, attention has been focussed on the possibility of increasing resistance through the use of a vaccine. A considerable body of knowledge relating to active immunity to the virus of poliomyelitis has grown up since the condition was first described in 1910. It was reviewed by Flexner in 1932.[28] Hope was kindled that a safe and effective method had been discovered by the independent publications of Brodie, and of Kolmer in 1935. These authors on the basis of rather limited observations on monkeys decided that they were justified in giving their respective methods a trial in human beings.

Brodie[29] used an emulsion of monkey-cord virus, treated with formalin the minimum amount of time necessary to render it non-infective for monkeys. Whether this treatment simply reduced the dose or modified the still living virus or whether it was no longer living could not be determined. Monkeys and children, injected subcutaneously with this material developed or showed an increase in neutralizing antibodies in their blood serum. As has since been pointed out, the demonstration of such substances in blood serum is not necessarily synonymous with neural immunity. Olitsky[29] and Schultz[27] independently found that monkeys vaccinated with this material and showing neutralizing antibodies in their blood serum were still susceptible to experimental infection by the intracerebral route.

A careful field trial of Brodie's vaccine was undertaken by the United States Public Health Service. Attempt was made to set up the test under carefully controlled conditions. Gilliam and Onstott[30] were unsuccessful in securing a sufficiently large experience to permit definite conclusions regarding the protective value of the procedure. They calculated that in an area where the control group were spared from epidemic prevalence, as were the children in the location in North Carolina and Virginia where this study was conducted, 7500 vaccinated children together with 7500 controls would have been necessary to show conclusively the value of a perfect vaccine against poliomyelitis. They were able to show, however, that Brodie's vaccine was relatively harmless, although they encountered a few very disturbing reactions.

Kolmer[31] used a 4% "remote" monkey passage virus treated with 1% sterile solution of sodium ricinoleate. He believed that through prolonged passage in monkeys his strain of virus had undergone some reduction in virulence for man, although he was unable to prove the point. He believed that it was further attenuated by the chemical treatment with sodium ricinoleate. Although he could infect monkeys by the intracerebral inoculation of 0.3 cc. of the vaccine, he failed in 42 attempts to infect monkeys by the subcutaneous injection of 0.5 cc.

per kilo, whereas in a series of 20 attempts with similar doses of fresh untreated virus paralysis developed in 1. He interpreted his experiments as indicating that the effect of sodium ricinoleate and later of the added preservative phenyl-mercuri-nitrate was one of devitalization or attenuation. The vaccine contained, nevertheless, living virus.

Following preliminary observation on 473 individuals to whom this material was given in Philadelphia, amounts totalling 22,022 cc. were distributed through 719 physicians for immunization of over 12,000 individuals. No attempt was made to measure the degree of protection afforded under natural conditions of exposure by comparison of carefully balanced test and control groups. Poliomyelitis developed in 10 individuals who had received 1 or 2 doses. Five of these were fatal. Kolmer[31] thought that some but not all of these were directly attributable to infection from the live virus in the vaccine.

Rivers[32] pointed out that Kolmer's experiments failed to prove that the virus contained in the vaccine emulsion had been decreased in infectivity any more than could be accounted for by dilution and the subcutaneous route of administration. Both he and Leake[33] presented convincing evidence that the cases of paralysis following the use of Kolmer's vaccine were in fact due to the inoculated living virus and not to coincident natural exposure. The method was therefore condemned as unsafe.

So far it has been impossible experimentally to confer immunity upon monkeys without giving them a clinical attack of the disease with its attendant risks. Whether the human species differs in this regard is yet to be ascertained. Epidemiologic data are interpreted as indicating that a vast majority of human beings are immunized by a subclinical attack. Whether the ingenuity of experimental investigators will be sufficiently great to develop a method which will imitate nature in this regard, and hold no risk of permanent neural damage, remains to be seen. In the meantime attention has been directed to a less dangerous procedure involving an effort to strengthen the barrier at the portal of entry.

Protective Effect of Intranasally Instilled Chemicals.—Armstrong and Harrison[34] found that if monkeys were treated by intranasal irrigation with 4% alum solution they offered a high degree of resistance against subsequent intranasal instillation of virus emulsion. Their observations were confirmed by Sabin, Olitsky and Cox[35] who add that protection is also afforded by 4% tannic acid. Schultz and Gebhardt[36] obtained similar results with picric acid, p-nitrophenol, trinitrolcresol and mercurochrome. The duration of this nonspecific protection is variable but can be maintained for some time if the treatments are repeated. In a later communication Armstrong and Harrison[37] confirmed and extended their earlier observations to include the effect of intranasal instillations of a considerable number of chemical solutions upon infection of mice with encephalitis virus and upon infection of monkeys with poliomyelitis. They found that intranasally instilled chemicals effective in the former were also effective in the latter. This facilitates further study of this question by the use of experimental encephalitis in mice. Picric acid, 0.32% to 0.64%, either alone or combined with alum, was found superior to 4% alum and the most satisfactory and efficient agent so far tried. The protective effect from spraying the nose of monkeys with this chemical solution was apparent

against intranasally inoculated poliomyelitis for at least 4 to 7 days following its last administration. It is believed that it exerts its protective effect locally either by rendering the mucous membranes less permeable to infection or possibly by direct action on the virus, or both.

In his most recent communication Armstrong[38] followed the ingenious experiment of Lennette and Hudson[39] in which they sectioned the olfactory tract of 5 monkeys and then inoculated them intravenously together with 5 intact controls. Four of the 5 controls succumbed to poliomyelitis, while the 5 animals whose olfactory tracts were sectioned remained well. In similar manner Armstrong gave intranasal instillations of 1.5 cc. of 0.32% picric acid in saline into each nostril of 9 monkeys. These 9 prepared and 9 nontreated control monkeys were then inoculated intravenously with poliomyelitis virus. Among the picric-acid-prepared animals there were 2 deaths due to poliomyelitis, while among the nine controls there were 6 deaths from poliomyelitis. The experiment was interpreted as indicating that picric acid instilled into the nostrils tends to protect monkeys *even against intravenous inoculations* and to confirm the conclusions of Lennette and Hudson regarding the importance of the nasal membranes and olfactory tract as a portal of entry.

As far as present information goes, the instillation of such a solution of picric acid into the nostrils of a human being is a harmless procedure. Whether it will afford the protection which is evident in monkeys remains to be determined—and incidentally is a much more difficult matter to prove. Even though the protection afforded be partial and temporary, it gives hope of at least reducing the number who suffer from clinical attacks of the disease during periods of unusual (epidemic) exposure.

KENNETH F. MAXCY, M.D.

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